Role of Surgery in Ovarian Carcinoma

Amanda Nickles Fader and Peter G. Rose

ABSTRACT

Surgery plays a critical role in the optimal management of all stages of ovarian carcinoma. In apparent early-stage ovarian cancer, a comprehensive surgical evaluation allows stratification of patients into low- and high-risk categories. Low-risk patients may be candidates for fertility-sparing surgery and can safely avoid chemotherapy and be observed. Treatment of patients with high-risk early- or advanced-stage ovarian cancer usually requires a combined modality approach. Although it is well known that epithelial ovarian cancer is moderately chemo-sensitive, what distinguishes it most from other metastatic solid tumors is that surgical cytoreduction of tumor volume is highly correlated with prolongation of patient survival. Procedures such as radical pelvic surgery, bowel resection, and aggressive upper abdominal surgery are commonly required to achieve optimal cytoreduction. Women who develop recurrent disease may be eligible for a secondary cytoreductive surgery or may require a surgical intervention to palliate disease-related symptoms. For women at high risk of ovarian cancer, prophylactic bilateral salpingo-oophorectomy significantly reduces the incidence of this disease. The purpose of this article is to provide a comprehensive review of the surgical management of ovarian carcinoma. The roles of primary, interval, and secondary cytoreductive surgeries; second-look procedures; and palliative surgery are reviewed. The indications for fertility-sparing and minimally invasive surgery as well as the current guidelines for prophylactic surgery in high-risk mutation carriers are also discussed.

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INTRODUCTION

Improvement in the 5-year survival of ovarian carcinoma patients has been observed in the last three decades as a result of both surgical and medical advances. Surgery is usually the initial treatment for women with suspected ovarian cancer. Accurate surgical staging and optimal tumor cytoreduction followed by platinum-based chemotherapy is the standard of care in the management of this disease and results in improved patient survival. Through an analysis of the applicable literature, we shall critically review the evidence on the surgical management of all stages of ovarian cancer in the primary and recurrent settings.

Aside from the discovery of an effective preventative strategy, the detection of patients with early-stage disease remains the greatest challenge in ovarian cancer. Proper identification of ovarian cancer among patients with a pelvic mass is aided by the imaging characteristics of the mass and abdomen and the preoperative serum CA-125 level. The Society of Gynecologic Oncology (SGO) and the American College of Obstetricians and Gynecologists (ACOG) referral guidelines for a newly diagnosed pelvic mass are listed in Table 1.1 Im et al2 retrospectively evaluated these guidelines at seven tertiary hospitals during a 12-month period. Among the 1,035 patients with pelvic masses who underwent surgical exploration, 30.7% had ovarian, tubal, or peritoneal carcinoma. On the basis of the SGO/ACOG guidelines, 70% of premenopausal patients and 94% of postmenopausal patients with ovarian cancer were correctly identified. Among premenopausal patients, reducing the critical value of CA-125 to 50 U/mL increased the sensitivity to 85%. Ideally, every patient with a pelvic mass who undergoes surgery should have the mass evaluated by a pathologist and should be consented for comprehensive staging in the event that malignancy is found.

The intent of the primary surgical procedure is to establish a diagnosis, assess the extent of disease, and remove as much gross tumor as possible. Although 75% of women with epithelial ovarian cancer will present with advanced disease, it is critical that the 25% of women diagnosed with early-stage disease undergo a comprehensive surgical staging procedure (Table 2). Comprehensive staging results in a shifting of patients with subclinical metastases from early- to advanced-stage disease with an improved median survival for both groups, also referred to as a “Will Rogers” phenomenon.3

An understanding of the spread pattern of epithelial ovarian cancer is critical when performing a surgical staging procedure. Ovarian cancer arises...
within the ovarian surface epithelium, grows focally, and ultimately breaches the ovarian capsule and metastasizes by exfoliation or by the abdominal/pelvic lymphatic system. Peritoneal fluid flows in a clockwise fashion; thus, cancer cells shed into the fluid initially implant throughout the pelvis and right paracolic gutters and across the right diaphragm and GI organs. Recognition of the importance of nodal metastases in clinically apparent early-stage ovarian cancer began in the mid-1970s. In a current series of 96 patients with gross disease confined to one ovary, Cass et al emphasized the significance of performing bilateral para-aortic lymph node sampling, as 30% of patients who underwent this procedure had contralateral nodal metastases only. Recently, Chan et al retrospectively analyzed 6,686 patients who underwent this procedure and discovered that women with stage I non-clear-cell ovarian cancers who underwent lymphadenectomy had a significant improvement in survival.

Surgical staging for ovarian carcinoma is typically performed through an abdominal incision that allows exposure of the entire abdomen. On entry into the peritoneal cavity, ascites is aspirated for cytology if present. If not present, cytologic washings of the pelvis and paracolic gutters are obtained. A total abdominal hysterectomy and bilateral salpingo-oophorectomy is performed in most patients. The contents of the peritoneal cavity, including all organs and peritoneal surfaces, are systematically inspected, and any suspicious-appearing areas are biopsied. Unless these areas are confirmed on frozen section to demonstrate malignancy, an omentectomy and peritoneal biopsies from the right and left pelvic peritoneum, cul-de-sac, bladder, paracolic gutters, and diaphragm are performed. Additionally, suspicious lymph nodes should be excised and sent for frozen section; if negative for malignancy, a pelvic and para-aortic lymphadenectomy should be performed to exclude microscopic disease. As 25% to 30% of patients with an intraoperative frozen section diagnosis of a borderline tumor will be diagnosed with an invasive cancer on final pathology, it is our practice to stage these tumors at the initial laparotomy.

After a thorough surgical evaluation, the staging system defined by the International Federation of Gynecology and Obstetrics (FIGO) is applied to guide adjuvant treatment decisions and determine the patient’s prognosis (Table 3). The importance of a comprehensive initial surgical procedure was illustrated by a multicenter national trial in which 100 patients with apparent stage I or II disease underwent surgical restaging. Thirty-three percent of patients were found to have more advanced disease at the second surgery. Histologic grade was a significant predictor of occult metastasis as 16% of patients with grade 1 tumors were upstaged compared with 46% with grade 3 disease.

### Table 1. SGO and ACOG Referral Guidelines for a Newly Diagnosed Pelvic Mass

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal (&lt; 50 years old)</td>
<td>CA-125 &gt; 200 U/mL, Ascites, Evidence of abdominal or distant metastasis (by exam or imaging study), Family history of breast or ovarian cancer (in a first-degree relative)</td>
</tr>
<tr>
<td>Postmenopausal (&gt; 50 years old)</td>
<td>CA-125 &gt; 35 U/mL, Ascites, Nodular or fixed pelvic masses, Evidence of abdominal or distant metastasis, Family history of breast or ovarian cancer (in a first-degree relative)</td>
</tr>
</tbody>
</table>

Abbreviations: SGO, Society of Gynecologic Oncology; ACOG, American College of Obstetricians and Gynecologists.

### Table 2. Comprehensive Staging Laparotomy in Apparent Early-Stage Ovarian Cancer

<table>
<thead>
<tr>
<th>Phase</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation</td>
<td>Unilateral or bilateral disease, Tumor on external surface of ovary, Capsule intact, Spill, Biopsies Any suspicious lesions, Pelvic peritoneum (3 biopsies), Cul-de-sac peritoneum, Right and left abdominal gutter, Undersurface of right diaphragm, Partial omentectomy, Para-aortic and pelvic nodes, Peritoneal washings</td>
</tr>
</tbody>
</table>

### Table 3. FIGO Staging of Primary Carcinoma of the Ovary

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>Growth limited to the ovary; no ascites. No tumor on the external surface; capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>Growth limited to both ovaries; no ascites. No tumor on the external surfaces; capsule intact</td>
</tr>
<tr>
<td>IC</td>
<td>Tumor either stage 1A or 1B but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension and/or metastases to the uterus and/or tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIC</td>
<td>Tumor either stage IIA or IIB with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involving one or both ovaries and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative</td>
</tr>
<tr>
<td>IIIB</td>
<td>Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative</td>
</tr>
<tr>
<td>IIIC</td>
<td>Abdominal implants more than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastasis equals stage IV</td>
</tr>
</tbody>
</table>

The management of early-stage ovarian carcinoma will be discussed elsewhere in this special issue of the Journal, but it is worth noting that comprehensively staged women with grade 3 disease or stage IC or greater are typically treated with platinum-based adjuvant therapy. Combining the results of two large European trials, patients with stage IA and IB (grades 2 and 3), stage IC, and stage II who received adjuvant chemotherapy after surgery had a significant improvement in progression-free and overall survival compared with those patients randomly assigned to observation. However, in an analysis of one of the studies, only the incompletely staged patients experienced improvements in survival. Controversies remain in the analysis of one of the studies, only the incompletely staged patients experienced improvements in survival. Controversies remain in the treatment of stage I ovarian cancer, especially for women with grade 2 tumors.

**FERTILITY-SPARING SURGERY**

In selected patients desiring fertility who have stage IA grade 1 or 2 ovarian tumors, unilateral salpingo-oophorectomy (USO) with inspection of the contralateral ovary and comprehensive staging is an option with a low risk of recurrence. In a recent series of 282 patients treated conservatively for invasive ovarian cancers, 113 became pregnant with 87 term deliveries. Thirty-three patients (12%) developed recurrence, and there were 16 disease-related deaths (4%). Conservative management of borderline tumors with cystectomy or USO may also be appropriate with risk of recurrence of 30% and 11%, respectively.

**PRIMARY CYTOREDUCTION OF ADVANCED-STAGE OVARIAN CARCINOMA**

Since the value of cytoreductive surgery was first recognized by Meigs in 1934 and validated by Griffiths in 1975, multiple retrospective studies have demonstrated that the amount of residual tumor after cytoreductive surgery correlates inversely with progression-free and overall survival (Table 4). In summarizing these studies, Carter noted that the median survival can be approximately doubled from 17 months to 39 months when cytoreductive efforts are successful. Although not seen in an earlier study, a more recent meta-analyses demonstrated that with each 10% increase in maximal cytoreduction, there was a 5.5% to 6.0% increase in median survival time was observed. Although the role of cytoreductive surgery in the treatment of advanced-stage ovarian cancer is well accepted, there is no randomized evidence supporting it. Two randomized, prospective trials were initiated in the United States and Holland in 1986 but were closed due to poor accrual because most investigators had a strong bias favoring surgery.

The majority of gynecologic oncologists are in agreement regarding the importance of an initial maximal cytoreductive effort, but the role of systemic pelvic and para-aortic lymphadenectomy in ovarian carcinoma staging for advanced disease is less clear. Burghardt et al noted that of all gynecologic malignancies, ovarian carcinoma has the highest rate of positive retroperitoneal nodes and reported a high frequency of persistent nodal disease after platinum-based chemotherapy in women who did not undergo lymphadenectomy during surgical staging. The authors theorized that the lymph nodes were chemotherapy-resistant sanctuaries and recommended that lymphadenectomy should be an essential component of the surgical management of ovarian cancer. However, in a recent randomized, prospective trial of 427 optimally debulked advanced ovarian cancer patients who were assigned to undergo systematic pelvic and para-aortic lymphadenectomy or resection of bulky nodes only, Benedetti-Panici et al demonstrated that patients who underwent systemic lymphadenectomy experienced improved progression-free but not overall survival while being put at risk for significantly longer operative times and blood loss. Also controversial is the role of cytoreduction in the treatment of stage IV patients. With the exception of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC-1) trial, which demonstrated that increased progression-free survival associated with optimal surgery is limited to patients with less advanced disease, recent data suggest that a significant survival advantage may be obtained for stage IV patients who undergo optimal cytoreduction, even in the presence of extrauterine disease.

The term optimal cytoreduction has been variably defined as having a maximal diameter of residual tumor of 0 to 3 cm. In a Gynecologic Oncology Group (GOG) study, Hoskins et al demonstrated that survival of patients with advanced ovarian cancer progressively decreased as the maximum residual disease increased from less than 0.5 to 2 cm (Fig 1). The GOG currently defines “optimal” as having residual tumor nodules each measuring 1 cm or less in

<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for Optimal Cytoreduction (cm)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffiths (1975)</td>
<td>0.6-1.5</td>
<td>18</td>
</tr>
<tr>
<td>Hacker (1983)</td>
<td>0.5-1.5</td>
<td>18</td>
</tr>
<tr>
<td>Vogl (1983)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Delgado (1984)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Pohil (1984)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Conte (1985)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Posada (1986)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Louie (1986)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Redman (1988)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Neji (1987)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Hainsworth (1987)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Piver (1988)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Seifer (1988)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Sutton (1989)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Omura (1989)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Bertelsen (1990)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Eisenkop (1992)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Hoskins (1994)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Munkarah (1997)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Michel (1997)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Bristow (1999)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Zang (2000)</td>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>Chi (2006)</td>
<td>0.5</td>
<td>29</td>
</tr>
</tbody>
</table>

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maximum diameter. This definition is likely to evolve given that increasing data demonstrates a further increase in survival for patients undergoing cytoreduction to less than 0.5 cm or no gross remaining disease. Alternatively, Vergote et al demonstrated significant differences in survival based on an estimation of the number of grams of residual disease: less than 1, 1 to 10, or more than 10 g. In an analysis of 433 patients with stage III and IV ovarian cancer who underwent primary cytoreduction, Stoeckle et al found that the number of residual nodules rather than their size was predictive of outcome. Additionally, published data suggest that if surgery is performed by physicians with training in gynecologic oncology, a survival advantage can be achieved when compared with surgery performed by general surgeons or generalist gynecologists.

TUMOR KINETICS AND PRIMARY CYTOREDUCTION

As described by Norton and Simon’s Gompertzian growth model, the growth fraction of the tumor (defined as the proportion of cells actively doubling during a given time frame) decreases as the volume of a tumor increases. Chemotherapeutic agents exert their maximum effect on smaller, actively proliferating tumors; thus cytoreductive surgery employed before systemic therapy results in improved chemotherapy response rates. Since chemotherapy kills cells by first-order kinetics, removing large masses increases the likelihood of complete tumor elimination with chemotherapy. However, the Goldie and Coldman model of spontaneous tumor cell mutation proposes that the larger the tumor, the more likely chemotherapy resistant clones will develop. Hacker et al demonstrated a poorer survival for patients whose initial metastatic tumor diameter exceeded 10 cm. However, data from several subsequent retrospective studies has demonstrated that optimal cytoreduction, more than the extent of initial disease, is a major determinant in patient outcomes. In addition to potentiating the effects of chemotherapy, maximal cytoreduction can also improve a patient’s quality of life by palliating disease-related symptoms caused by tumor burden.

RADICAL DEBULキング PROCEDURES

Surgery performed for advanced-stage ovarian cancer commonly requires the addition of complex procedures such as radical pelvic surgery, bowel resection, removal of diaphragmatic disease or splenectomy to substantially decrease the tumor burden. Prospective and retrospective studies suggest that the need for aggressive surgical resection does not necessarily indicate a poor prognosis for patients (once the outcomes are adjusted for residual disease). Moreover, these studies report acceptably low morbidities associated with the performance of radical procedures.

A recent survey of SGO members identified that tumor involving the diaphragm, bowel mesentery, and portal triad consistently
Role of Surgery in Ovarian Carcinoma

Modern surgical tools have facilitated aggressive tumor resection during cytoreductive surgery, including the cavitational ultrasonic surgical aspirator, the argon beam coagulator, the carbon dioxide laser, and the loop electrosurgical excision procedure. Retrospective data from several series demonstrates the usefulness of these instruments in the resection of metastases in vascular or anatomically complex regions of the abdomen, such as the diaphragm and liver.65-70

Among patients requiring intestinal resection to achieve optimal cytoreduction, sigmoidectomy is the most commonly required procedure (56%).21 This results in a short rectal stump below the peritoneal reflection. Contemporary stapling devices, such as the End to End (EEA) stapler, allow very low anastomoses, avoiding colostomies for these women. Several retrospective series on the role of bowel resection in ovarian cancer surgery are reviewed in Table 5.71-76

The effects of aggressive surgical resection of upper abdominal ovarian metastases, including diaphragmatic, hepatic, and splenic disease, were recently studied in several retrospective reviews, also summarized in Table 5.80-84 In a report of 144 patients with carcinoma, 67.5% of which experienced optimal (< 1 cm) cytoreduction, residual disease and the performance of radical procedures (defined as diaphragmatic surgery, bowel resection, splenectomy, or extensive peritoneal stripping) were the only independent predictors of survival on multivariate analysis.74

### Table 5. Complication Rates of Radical Surgical Debulking Procedures Performed During Primary or Secondary Cytoreductive Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Optimal (%)</th>
<th>Surgery</th>
<th>Morbidity* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Bowel resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gillette-Cloven (2001)</td>
<td>105</td>
<td>33</td>
<td>Primary</td>
<td>59</td>
</tr>
<tr>
<td>Mourton (2005)</td>
<td>70</td>
<td>NR</td>
<td>Primary</td>
<td>60</td>
</tr>
<tr>
<td>Hoffman (2005)</td>
<td>144</td>
<td>100</td>
<td>Primary</td>
<td>19</td>
</tr>
<tr>
<td>Aletti (2006)</td>
<td>57</td>
<td>NR</td>
<td>Primary</td>
<td>12</td>
</tr>
<tr>
<td>Estes (2006)</td>
<td>48</td>
<td>52</td>
<td>Primary</td>
<td>27</td>
</tr>
<tr>
<td>Tebes (2006)</td>
<td>125</td>
<td>75</td>
<td>Both</td>
<td>37</td>
</tr>
<tr>
<td>Upper abdominal resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cliby (2004)</td>
<td>41</td>
<td>NR</td>
<td>Both</td>
<td>19.5</td>
</tr>
<tr>
<td>Aletti (2006)</td>
<td>194</td>
<td>67.5</td>
<td>Primary</td>
<td>NR</td>
</tr>
<tr>
<td>Eisenhauer (2006)</td>
<td>57</td>
<td>100</td>
<td>Primary</td>
<td>12</td>
</tr>
<tr>
<td>Splenectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magtibay (2006)</td>
<td>112</td>
<td>NR</td>
<td>Both</td>
<td>23</td>
</tr>
<tr>
<td>Manci (2006)</td>
<td>24</td>
<td>100</td>
<td>Secondary</td>
<td>33</td>
</tr>
</tbody>
</table>

*All major perioperative morbidity (includes intraoperative complication, hemorrhage > 1,500 mL, blood transfusion, abdominal/pelvic abscess, pneumonia, sepsis, pulmonary embolus, cardiovascular event, bowel-related morbidity or need for reoperation within 30 days of surgery) and bowel-related morbidity (includes prolonged ileus > 10 days, perforated viscous, anastomotic leak, bowel obstruction, short bowel syndrome or intraoperative morbidity resulting from bowel surgery).

†Mortality resulting from all causes, within 30 days of surgery.

According to SEER and single-institution data, approximately 48% of ovarian cancer patients are older than 65% and 7% are older than 80 years of age.65,86 Many factors potentially limit the therapeutic options for elderly patients, including comorbid disease, decreased functional status, limitations in financial resources and social support, and assumed inability to tolerate treatment.86-89 Thus, ovarian cancer in elderly patients, and particularly the extreme elderly (>80 years), is frequently undertreated.90

Surgery in particular has often been considered too risky for the elderly patient. Yet many studies attest that surgical procedures can be performed safely in women older than 65 years.91-96 Contemporary reports from Wright et al99 and Sharma et al100 found no significant relationship between perioperative complications and type of procedure, elderly age, comorbidities, or transfusions. Irrespective of age, those patients who underwent optimal cytoreduction experienced a significantly longer survival than patients who were not. However, few studies have examined perioperative patient variables that could place select elderly ovarian cancer patients at risk for poor surgical outcomes. Alphs et al107 identified women 80 years of age and older with poor nutritional status (ie, serum albumin < 3.7 g/dL) as having a greater risk of suboptimal surgery and poor survival outcome than their age-matched, nutritionally sound cohorts. Because elderly ovarian cancer patients have been grossly under-represented in most clinical trials, the optimal therapy for this population is not established. Most available studies are small and retrospective, and bias exists in

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choosing treatments. Nevertheless, the surgeon must use judgment on the extent of the operation an elderly or high-risk patient can tolerate.

**INTERVAL DEBULKING SURGERY**

The term “interval debulking surgery” has been used to refer to two clinical scenarios: secondary surgical debulking after initial suboptimal cytoreduction or primary surgical debulking after neoadjuvant chemotherapy. Interval debulking surgery after suboptimal primary cytoreduction and induction chemotherapy is a strategy for further reducing tumor burden. Such an approach is supported by several small retrospective studies and a large randomized trial by the European Organisation for the Research and Treatment of Cancer (EORTC).98 In this prospective trial, 278 suboptimally debulked ovarian cancer patients with stable or responding disease after three cycles of cisplatin and cyclophosphamide were randomly assigned to interval debulking surgery or no surgery followed in both arms by three additional cycles of chemotherapy. The group that underwent surgery experienced a significant survival advantage, with surgery reducing the risk of death by 33% (P = .008).

By contrast, a subsequent GOG study did not confirm the benefit of secondary surgical debulking in platinum-responsive patients who underwent suboptimal cytoreduction.99 In this trial, 550 patients with stage III to IV ovarian cancer treated with three cycles of cisplatin and paclitaxel were randomly assigned either to an interval debulking surgery or no surgery followed in both arms by three additional cycles of chemotherapy. There were no significant differences in progression-free or overall survival between the two groups. One difference between the studies was that the GOG trial required that all patients had undergone an attempt at primary optimal debulking, and in the majority of cases (95%), this was performed by a board-certified gynecologic oncology surgeon. The surgical experience of the primary surgeon was not as strictly defined for the EORTC study, and because of this discrepancy, a greater percentage of patients underwent suboptimal cytoreduction and more patients had larger (> 5 cm) residual disease before initiating chemotherapy. Clinicians might, therefore, argue that interval debulking surgery has a place in patients whose primary surgery was not performed in an ideal setting.

The term interval debulking surgery has also been utilized for patients undergoing neoadjuvant chemotherapy followed by primary surgical debulking and additional chemotherapy. This scenario is best referred to as neoadjuvant chemotherapy and has been advocated for the treatment of high-risk surgical candidates. Recently, a nonrandomized report by Elit et al100 examined the outcomes of 2,502 Canadian women with ovarian cancer treated from 1998 to 2002 with primary cytoreductive surgery followed by chemotherapy, neoadjuvant chemotherapy followed by interval debulking surgery, or chemotherapy alone. Survival was most improved for patients treated with primary surgery and adjuvant chemotherapy followed by primary chemotherapy with adjuvant surgery compared with patients treated with chemotherapy alone. It is possible that neoadjuvant chemotherapy patients who undergo interval surgery are self-selected on the basis of their favorable response to chemotherapy.

A randomized European trial (EORTC 51971) comparing primary surgery plus chemotherapy to neoadjuvant chemotherapy with subsequent surgery is underway. To date, retrospective data suggest that progression-free survival for patients who have a complete response to chemotherapy is considerably shorter for those with bulky disease present at the initiation of chemotherapy.101

**SECOND-LOOK SURGERY**

Second-look laparotomy is a surgical re-evaluation of asymptomatic ovarian cancer patients who have no clinical evidence of tumor after primary cytoreductive surgery and adjuvant chemotherapy. The procedure involves a systematic examination of the peritoneal cavity and retroperitoneal space. Because predictors such as CA-125 and radiographic studies are not sufficiently accurate to determine a complete response to chemotherapy in women with ovarian cancer, this procedure was initially used to verify disease status and establish an end point for chemotherapy treatment.102

Residual disease is found in more than 50% of women with advanced ovarian cancer who have achieved an apparent clinical remission with chemotherapy.103 The presence of disease at second-look laparotomy is associated with a poorer prognosis than finding no disease. However, complete resection of disease, if present, is associated with improved survival.104 The routine performance of second-look procedures is not recommended. Results from an Australian trial and an American GOG trial failed to demonstrate a survival benefit despite earlier initiation of therapy when recurrent disease was found.105,106 Thus, second-look laparotomy is best limited to experimental protocols.

**SURGICAL MANAGEMENT OF RECURRENT OVARIAN CANCER**

**Secondary Cytoreductive Surgery**

Despite aggressive front-line therapy with primary surgery and adjuvant chemotherapy, the majority of women with advanced ovarian cancer will develop recurrent disease. The standard management of patients with recurrence, particularly the role of surgery, remains poorly defined. Secondary cytoreductive surgery is a subsequent surgical debulking after primary treatment and a treatment-free interval. Although the studies are retrospective, they suggest that the longer the progression-free interval after primary treatment, the less residual disease the patient had following primary surgery, and the better the patient’s performance status, the more likely that the patient will benefit from secondary cytoreductive surgery.107-126

The importance of the treatment-free interval is demonstrated in a retrospective series of 33 advanced ovarian cancer patients who benefited little from a secondary debulking after progression on first-line chemotherapy.127 Most studies demonstrate an improvement in survival for patients who had complete resection of recurrent disease with a secondary debulking surgery (Table 6)128,129 and whose treatment-free interval was greater than 12 months.103 In a series of 55 advanced ovarian cancer patients, Salani et al130 reported that a diagnosis-to-recurrence interval of at least 18 months, the presence of only one or two recurrence sites on preoperative imaging studies and complete secondary surgical cytoreduction (achieved in the majority of patients) were associated with a median postrecurrence survival of approximately 50 months. Although the value of secondary cytoreduction in women with recurrent epithelial ovarian cancer is still
uncertain because of the absence of prospective randomized data, it may be considered in select patients with good response to first-line chemotherapy, a limited number of recurrent disease sites, and a good performance status. These issues will be studied in an upcoming GOG trial (GOG 213).

Palliative Surgery

The goal of palliative surgery for ovarian cancer is to improve the quality of life of patients that usually have a limited life expectancy. The most common indication for a palliative procedure is malignant intestinal obstruction. The management of malignant obstruction is challenging, not only because it usually occurs in the setting of recurrent, often drug-resistant ovarian cancer, but also because there is a high morbidity and mortality associated with surgery. In a Cochrane Database Review, Feuer et al established that no conclusions could be drawn from the many retrospective case series on intestinal obstruction in gynecologic cancers. Control of symptoms and reobstruction rates varied considerably among studies, and a wide range of postoperative morbidity and mortality was also reported. Although carefully selected, potentially chemotherapy-sensitive patients with good performance statuses may be considered for palliative procedures, the role of surgery in malignant bowel obstruction requires further investigation, using validated outcome measures.

Risk-Reducing Surgery in Hereditary Gynecologic Cancer Syndromes

Approximately 10% of epithelial ovarian cancers occur as a result of inherited mutations and usually arise earlier than do ovarian cancers caused by sporadic mutations. Women with known tumor suppressor gene mutations in the BRCA1 and BRCA2 genes have a high risk of developing both ovarian and breast cancers. There is substantial prospective and retrospective data supporting the role of risk-reducing salpingo-oophorectomy (RRSO) in the prevention of ovarian cancer. Initial retrospective studies and decision-analysis models have recently been validated by three large trials, summarized in Table 7, confirming the beneficial effect of RRSO on reduction in ovarian cancer rates.

Hereditary nonpolyposis colorectal cancer syndrome (HNPCC) is a second familial disorder that increases a woman’s risk of...
ovarian as well as uterine and gastrointestinal cancers. Schmeler et al., in a retrospective study of 315 women with documented HNPCC-associated mutations, reported no cases of endometrial or ovarian cancer among the women who had undergone prophylactic hysterec- tomy and/or bilateral salpingo-oophorectomy compared with 33% and 5%, respectively, of control group subjects (Table 7).

Recently, a joint task force of the American Society of Clinical Oncology and the Society of Surgical Oncology concluded that the evidence overwhelmingly supports RRSO as the best available strategy to decrease the incidence of and mortality from ovarian cancer in BRCA mutation carriers. Furthermore, most experts believe that risk-reducing hysterectomy and bilateral salpingo-oophorectomy do have a role in the management of women with HNPCC.

Minimally Invasive Surgery

The role of laparoscopy in ovarian cancer is evolving but is currently utilized for the evaluation of the complex adnexal mass, for staging or (restaging) of apparent early ovarian cancer, and to determine the operability of an advanced cancer. Less than 5% of masses managed by laparoscopy will, in fact, be malignant; however, a surgeon who chooses to evaluate an adnexal mass laparoscopically should discuss the possibility of cancer and its surgical implications with the patient preoperatively, have a pathologist immediately available to perform frozen section analysis if necessary, and have a low threshold for converting to laparotomy if a malignancy is confirmed. Ideally, laparotomy should be deferred until a surgeon experienced in ovarian cancer staging is available. Immediate referral to a gynecologic oncologist is also recommended to avoid delays in postoperative treatment.

A concern with laparoscopic management of an adnexal mass is intraoperative rupture, although this complication is possible with laparotomy as well. The literature reports many cases of intraperito- neal tumoral dissemination after laparoscopic rupture of an apparent early-stage ovarian cancer. The impact of iatrogenic tumoral rupture is controversial; however, in patients without any other evidence of extrasophageal disease, it may be the only reason that adjuvant chemotherapy is indicated.

It is also possible for patients with apparent early-stage ovarian cancer to be comprehensively staged using laparoscopy, depending on the skill of the surgeon. In an evaluation of 50 patients who underwent comprehensive staging by either laparoscopy or laparotomy for apparent stage I ovarian or fallopian tube cancers, Chi et al. found that all patients had similar complication rates and clinical outcomes irrespective of the staging technique used. Leblanc et al. reported their experience with laparoscopic re- staging of patients with adnexal malignancies referred by general gynecologists or surgeons. Forty-two of 43 patients were restaged laparoscopically, and eight patients (19%) were upstaged and received chemotherapy as a result. After a 54-month median follow-up, three (6.4%) of the 34 remaining patients diagnosed as stage IA, grade 1 and 2, experienced disease recurrence and died.

Laparoscopy may also be a tool for excising isolated recurrent metastases and evaluating the operability of a cancer primarily or in the setting of recurrent disease. Recent reports have found diagnostic laparoscopy before primary cytoreduction and second-look laparos- copy to be safe and accurate methods of assessing intraperitoneal disease status.

CONCLUSION

From a surgical perspective, the continuing challenges for gynecologic oncologists are to optimize patient selection for primary cytoreductive surgery, to determine which patients might benefit from interval or secondary cytoreduction, to continue the development of better surgical techniques, and to minimize perioperative morbidity and morality. Surgery is of great value in the treatment of epithelial ovarian cancer, especially for patients who can undergo optimal cytoreduction. A primary surgical procedure leading to minimal or no residual disease is one of the best weapons currently available to physicians for combating this deadly disease. Considerable evidence also demonstrates that secondary cytoreduction is advantageous in select pa- tients. The importance of adjuvant chemotherapy in the treatment of ovarian cancer cannot be minimized, as cytoreductive surgery is most beneficial in patients with chemotherapy-sensitive disease. Nevertheless, referral of patients with apparent ovarian cancer to gynecologic oncologists for primary surgery may be one of the best strategies currently available for improving overall survival.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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