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REVIEW ARTICLE

Role of Surgery in Ovarian Carcinoma

Amanda Nickles Fader and Peter G. Rose

From the Cleveland Clinic, Cleveland, OH.

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Address reprint requests to Peter G. Rose, MD, Cleveland Clinic Foundation, 9500 Euclid Ave, A-81, Cleveland, OH 44195; e-mail: rosep@ccf.org.

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A B S T R A C T

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 chemosensitive, 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 preventive 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 al[2] 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

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

Age Group
Premenopausal (< 50 years old)
CA-125 > 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)
Postmenopausal (> 50 years old)
CA-125 > 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)

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

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[4] 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[5] retrospectively analyzed 6,686 women with clinical stage I ovarian cancer from the Surveillance, Epidemiology, and End Results (SEER) program between 1988 and 2001 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.

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

Phase
Evaluation
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

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.[6] 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 3. FIGO Staging of Primary Carcinoma of the Ovary

Stage	Criteria
I	Growth limited to the ovaries
IA	Growth limited to the ovary; no ascites. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites. No tumor on the external surfaces; capsule intact
IC	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
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC	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
III	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
IIIA	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
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative
IIIC	Abdominal implants more than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant mestastasis. 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

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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.[7] However, in an analysis of one of the studies, only the incompletely staged patients experienced improvements in survival.[8] 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%).[9] Conservative management of borderline tumors with cystectomy or USO may also be appropriate with risk of recurrence of 30% and 11%, respectively.[10]

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).[11-36] In summarizing these studies, Carter[37] 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, a 5.5% to 6.0% increase in median survival time was observed.[30,38] 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.[39]

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[40] 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.[41] 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,[42] recent data suggest that a significant survival advantage may be obtained for stage IV patients who undergo optimal cytoreduction, even in the presence of extraperitoneal disease.[34,35,43,44]

The term optimal cytoreduction has been variably defined as having a maximal diameter of residual tumor of 0 to 3 cm.[13,14,22,24,38] In a Gynecologic Oncology Group (GOG) study, Hoskins et al[29] 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 4. Effect of Residual Tumor After Primary Cytoreduction on Survival of Advanced-Stage Ovarian Cancer Patients Treated With Adjuvant Chemotherapy

Study	Criteria for Optimal Cytoreduction (cm)	Median Survival (months)	
		Optimal	Suboptimal
Griffiths (1975)[12]	0.6-1.5	18	11
	< 0.5	29	
	0	39	
Hacker (1983)[13]	0.5-1.5	18	6
	< 0.5	40	
Vogl (1983)[14]	≤ 2	40	16
Delgado (1984)[15]	< 2	45	16
Pohl (1984)[16]	< 2	55	18
Conte (1985)[17]	< 2	25	14
Posada (1985)[18]	< 2	30	18
Louie (1986)[19]	< 2	24	15
Redman (1986)[20]	< 2	37	26
Neijt (1987)[21]	< 2	40	21
Hainsworth (1988)[22]	≤ 3	72	21
Piver (1988)[23]	≤ 1	48	21
Seifer (1988)[24]	≤ 2	29	11
Sutton (1989)[25]	< 3	45	23
Omura (1989)[26]	0	48	21
Bertelsen (1990)[27]	< 2	30	18
Eisenkop (1992)[28]	< 1	31	18
Hoskins (1994)[29]	≤ 1	36	16
Munkarah (1997)[32]	≤ 2	25	15
Michel (1997)[33]	< 2	24	14
Bristow (1999)[34]	≤ 1	38	10
Zang (2000)[35]	≤ 1	19	8
Chi (2006)[36]	1-2	33	34
	0.6-1	48	
	≤ 0.5	66	
	0	106	

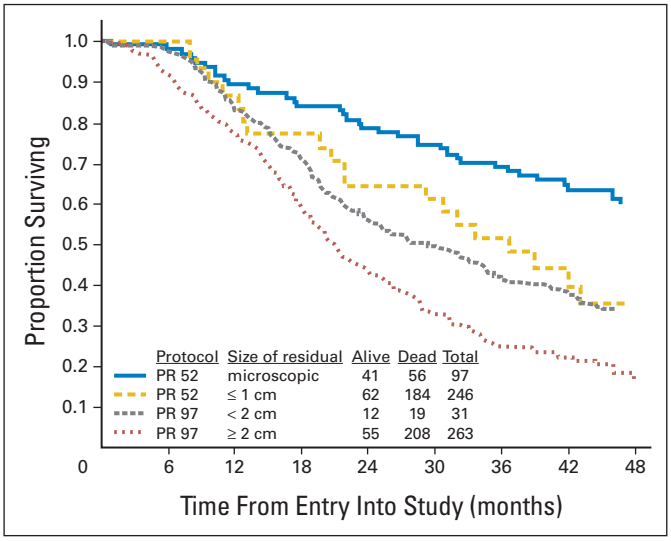

Fig 1. Survival related to maximum residual disease less than 2 cm. Reprinted with permission.[29]

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.[38] Alternatively, Vergote et al[45] 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[46] 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.[48]

PREOPERATIVE PREDICTORS OF OPTIMAL CYTOREDUCTION

Several investigators have attempted to define laboratory or radiographic parameters that indicate a low likelihood of achieving optimal cytoreduction in the primary setting. However, studies describing an association between the preoperative serum CA-125 level and the ability to predict surgical cytoreductive outcome have accuracy rates of only 50% to 78%.[49-52] In an effort to identify preoperative radiologic criteria that predict for suboptimal cytoreduction, Bristow et al[53] designed a model with 13 radiographic features on computed tomography (CT) and performance status with 93% accuracy for predicting cytoreductive status. Additionally, Dowdy et al[54] observed that only one radiographic feature on CT—diffuse peritoneal thickening—independently predicted suboptimal cytoreduction. However, in a recent multi-institution reciprocal validation study of CT predictors of suboptimal cytoreduction in primary advanced ovarian cancer patients, Axtell et al[55] demonstrated not only that the high accuracy rates of CT predictors in the above studies could not be validated in their own retrospective cohort of patients, but also that an independent CT predictive model designed by the authors could not be applied to the patient cohorts from the other two studies. To date, no single preoperative predictor has demonstrated sufficient accuracy to definitively utilize in making decisions between surgical cytoreduction and neoadjuvant chemotherapy. Until prospective studies confirm otherwise, laboratory and radiographic criteria should be considered only in the context of all other preoperative features.

Alternatively, it is possible that clinical outcomes have more to do with tumor biology than with cytoreductive status, with less aggressive tumors being more amenable to resection or intrinsically sensitive to chemotherapy. Although there are conflicting data regarding the ability of microarray gene profiles to predict optimal surgical cytoreduction, with time, improved knowledge of the genetic basis of ovarian cancer may enable us both to individualize medical therapy and to determine which patients will benefit most from surgical interventions.[56,57] Nevertheless, retrospective studies suggest that optimal residual disease remains an important prognostic variable, regardless of whether it was obtained with simple or extensive surgery.[58] In fact, unlike tumor stage or grade, residual disease is the only modifiable prognostic variable in ovarian cancer, although the prognosis for stage IIIC patients who underwent optimal cytoreduction remains poorer than for that of patients with stage IIIA or IIIB.[59]

TUMOR KINETICS AND PRIMARY CYTOREDUCTION

As described by Norton and Simon's Gompertzian growth model, [60] 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.[61] 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[61] proposes that the larger the tumor, the more likely chemotherapy resistant clones will develop. Hacker et al[13] 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.[34,36,37] 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 DEBULKING 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).[63] 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

precluded optimal cytoreduction.[64] 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%).[71] 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 collective bowel-related morbidity from combined studies is acceptable but certainly not inconsequential, ranging from 2% to 30.5%. Anastomotic leak after rectosigmoid resection and primary anastomosis is a serious complication. Although most patients can avoid diverting stomas and undergo primary anastomosis with a low complication rate, Richardson et al[77] recently reported that patients with a low serum albumin level ($\leq$2.4 g/dL) are at increased risk for anastomotic leak and may benefit from a protective diverting colostomy/ileostomy. A study on US patterns of surgical care for ovarian cancer by Goff et al[78] recently reported that colostomies were performed by general surgeons in 23.1% and by gynecologic oncologists in 2.7% of cases ($P < .001$). In addition, Abdul et al[79] identified significant preoperative factors associated with increased risk of bowel resection including secondary surgery, symptoms of bowel disturbance, FIGO stage III/IV disease and CA-125 levels of at least 2,500 U/mL.

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 carcinomatosis, 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]

ELDERLY OR HIGH-RISK SURGICAL CANDIDATE

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.[85,86] 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 ($\geq$ 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 al[95] and Sharma et al[96] 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 al[97] 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

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

Study	Patients	Optimal (%)	Surgery	Morbidity* (%)		Mortality† (%)
				Overall	Bowel Related	
Bowel resection						
Gillette-Cloven (2001)[72]	105	33	Primary	59	27	5.7
Mourton (2005)[73]	70	NR	Primary	60	5.7	1.4
Hoffman (2005)[71]	144	100	Primary	19	2.8	0
Aletti (2006)[74]	57	NR	Primary	12	3.4	0
Estes (2006)[75]	48	52	Primary	27	2	4
Tebes (2006)[76]	125	75	Both	37	30.5	2.4
Upper abdominal resection						
Cliby (2004)[80]	41	NR	Both	19.5		0
Aletti (2006)[81]	194	67.5	Primary	NR		1.5
Eisenhauer (2006)[82]	57	100	Primary	12		NR
Splenectomy						
Magtibay (2006)[83]	112	NR	Both	23		5
Manci (2006)[84]	24	100	Secondary	33		0

*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.

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 al[100] 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 55971) comparing primary surgery plus chemotherapy to neoadjuvant chemotherapy with subsequent surgery is underway. To date, retrospective data suggests 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 al[130] 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

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Table 6. Secondary Cytoreduction in Patients With Recurrent Ovarian Cancer

Study	Patients	Criterion (cm)	% Undergoing Cytoreduction	Survival (months)		*P*
				Optimal	Suboptimal	
Berek (1983)[107]	32	< 1.5	38	20	5	< .01
Morris (1989)[108]	30	< 2	57	18	13	> .05
Janicke (1992)[109]	30	0	47	29	9	.007
Segna (1993)[110]	100	< 2	61	27	9	.0001
Pecorelli (1994)[111]	27	< 2	58	20	12	.045
Vaccarello (1995)[112]	38	< 0.5	37	NR	23	< .0001
Cormio (1999)[113]	21	0	71	32	9	.02
Gadducci (2000)[114]	30	0	57	37	19	.04
Zang (2000)[115]	106	< 1	43	20	8	< .0001
Eisenkop (2000)[116]	106	0	82	44	19	.007
Munkarah (2001)[117]	25	< 2	72	57	15	.08
Scarabelli (2001)[118]	149	≤ 1	70	32	12	< .001
Tay (2002)[119]	46	0	41	38	11	.002
Gronlund (2005)[120]	38	0	42	52	20	.009
Onda (2005)[121]	44	0	59	52	20	.0007
Gungor (2005)[122]	44	0	77	19	9	.007
Pfister (2005)[123]	267	0	50	45	19	.0001
Ayhan (2006)[124]	64	< 1	39	28	18	.004
Chi (2006)[125]	157	≤ 0.5	52	56	27	.001
Benedetti-Panici (2006)[126]	47	< 1	41	61	10	

Modified from Hauspy J, Covens A: Cytoreductive surgery for recurrent ovarian cancer. Curr Opin Obstet Gynecol 19:15-21, 2007, with permission.[129]

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[131] 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.[132-135] 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

Table 7. RRSO Decreases Incidence and Mortality Resulting From Ovarian Cancer

Study	Type	BRCA 1/2/HNPCC Mutation Carriers	Mutation Carriers		Follow-Up Period (years)	Reduction in Cancer Risk With RRSO (%)	Hazard Ratio	95% CI	Peritoneal Cancer Rates Post-RRSO (%)
			RRSO	Surveillance					
Kauff (2002)[133]	Prospective	170*	98	72	2	75	0.25	0.08 to 0.74	1
Rebbeck (2002)[134]	Retrospective	551*	259	292	9	96	0.04	0.01 to 0.016	0.8
Finch (2006)[135]	Prospective	1828*	1,045	783	3.5	80	0.20	0.07 to 0.58	4
Schmeler (2006)[136]	Retrospective	315†	47	223	2	100	—	62 to 100	0

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; HNPCC, hereditary nonpolyposis colorectal cancer syndrome.
*BRCA 1/2.
†HNPCC.

ovarian as well as uterine and gastrointestinal cancers. Schmeler et al,[136] 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 hysterectomy 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.[137] Furthermore, most experts believe that risk-reducing hysterectomy and bilateral salpingo-oophorectomy does 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.[138]

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.[138] 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.[139,140]

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 intraperitoneal tumoral dissemination after laparoscopic rupture of an apparent early-stage ovarian cancer.[141,142] The impact of iatrogenic tumoral rupture is controversial; however, in patients without any other evidence of extraovarian 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.[142] 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[143] found that all patients had similar complication rates and clinical outcomes irrespective of the staging technique used.

Leblanc et al[144] reported their experience with laparoscopic restaging 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 laparoscopy to be safe and accurate methods of assessing intraperitoneal disease status.[145-150]

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 mortality. 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 patients. 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.

AUTHOR CONTRIBUTIONS

Conception and design: Amanda Nickles Fader, Peter G. Rose
Administrative support: Amanda Nickles Fader, Peter G. Rose
Collection and assembly of data: Amanda Nickles Fader, Peter G. Rose
Data analysis and interpretation: Amanda Nickles Fader, Peter G. Rose
Manuscript writing: Amanda Nickles Fader, Peter G. Rose
Final approval of manuscript: Amanda Nickles Fader, Peter G. Rose

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There are several types of ovarian carcinoma, but epithelial ovarian carcinoma (EOC) is the most frequent one, representing 95% of ovarian cancers. The rest of them develop from other ovarian cells (germ cell tumours and sex cord-stromal tumours) [4]. EOC is also the most frequent cause of death from gynaecological neoplasia [5, 8â€“10].Â 4. Romanidis K, Nagorni EA and Halkia E et al (2014) The role of cytoreductive surgery in advanced ovarian cancer: the general surgeonâ€™s perspectiva J BUON 19(3) 598â€“604 PMID: 25261641. 5. Van Driel WJ, Lok CA and Verwaal V et al (2015) The role of hyperthermic intraperitoneal intraoperative chemotherapy in ovarian cancer Curr Treat Options Oncol 16(4) 14 DOI: 10.1007/s11864-015-0329-5 PMID: 25796375. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe dâ€™Investigateurs Nationaux Pour les Etudes des Cancers de lâ€™Ovaire (GINECO).Â The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. Cancer. 2000; 188: 144-153. The goal of the surgery in ovarian cancer is to obtain a complete cytoreduction. Figure 2. Goal of the surgery in ovarian cancer. Chang and Bristow in 2012, reported a single institution series and cooperative group trials since 2003 of patients who underwent primary debulking surgery followed by adjuvant cheâ€ motherapy. Over 14000 patients in 15 studies were analyzed.[32] A marked inverse correlaâ€ tion between the maximal diameter of residual tumor and OS was noted.Â [61] Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surâ€ gery in the treatment of pa- tients with recurrent epithelial ovarian carcinoma. Canâ€ cer. 2000;88:144-53. 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.