Surgical Management of Epithelial Ovarian Cancer

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ABSTRACT

Epithelial ovarian cancer is the sixth most common cancer in women in the US and still remains the most lethal of gynecologic cancers. Diagnosis at an advanced stage and development of resistance to chemotherapy, despite remarkable initial chemosensitivity, account for the grim overall prognosis in these patients. Surgery still remains the cornerstone for the diagnosis and the management of this disease. In patients with apparently early disease, it is critical to perform thorough surgical staging to define the subset of patients who would benefit from adjuvant chemotherapy. Preservation of the uterus and the uninvolved contralateral adnexa is acceptable in selected patients. In advanced disease, aggressive cytoreductive surgery is associated with improved response to chemotherapy, prolonged disease-free survival, and overall survival. The timing of debulking and the extent of debulking are discussed.

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INTRODUCTION

The American Cancer Society estimates that ovarian cancer is diagnosed in 25,000 American women each year and 14,000 die of this disease annually.[1] Because recurrent disease has developed resistance to chemotherapy, the 5-year survival of ovarian cancer still remains grim.[2] However, important advances have been made in the short- and mid-term survival of ovarian cancer. In approximately two of every three women with ovarian cancer, the disease is diagnosed at an advanced stage, which reflects the lack of effective screening tools for the early detection of ovarian cancer. Even CA-125, the best serum marker available to the clinician, is not elevated in roughly half of stage I ovarian cancers,[3] and its elevation in premenopausal women is almost meaningless. The combined use of CA-125 marker screening and pelvic ultrasound can detect subclinical ovarian cancers, but more than half of these cases are already stage III diseases.[4,5] Intense investigative work is currently ongoing to identify valuable serum markers for the early detection of ovarian cancer.

Surgery still remains the cornerstone for the diagnosis and the management of this disease.[6] The present review will summarize both the theoretical rationale and the accumulated clinical experience supporting the fundamental role of surgery in the management of ovarian cancer and will present different approaches that are available for the treatment of this disease.

APPARENTLY EARLY EPITHELIAL OVARIAN CANCER

Rationale for staging

Approximately 20% of ovarian cancers are limited to the ovaries at presentation (stage I), while in another 15%, the tumor extends locally within the pelvis (stage II). Of patients with cancer that appears confined to the ovaries at initial exploration, 35% will be given a higher stage after surgical exploration and staging. Approximately 15% of patients with apparent stage I disease will be given a higher stage on the basis of peritoneal cytology results,[7] another 7% will have occult disease in the peritoneum or the omentum, and 13% will be given a higher stage on the basis of results from retroperitoneal pelvic or aortic lymph node dissection. Nearly half of patients with occult metastatic disease experience tumor recurrence. Because adjuvant platinum-based chemotherapy has been proven to extend the progression-free interval in patients at high risk, surgical staging provides critical information which affects the outcome of the disease.[8,9] Yet, too often the

EDUCATIONAL OBJECTIVE

Obtain an overview of the available options in the surgical management of epithelial ovarian cancer.

TALKING POINTS	Physicians	Pharmacy	Formulary	Cancer Nurses

A patient with clinical findings suggestive of ovarian cancer should be referred for surgery to a a formally trained gynecologic oncologist, as statistics show that she will receive superior care and have a better outcome.

Optimal surgical cytoreduction is associated with better response to chemotherapy.

Neoadjuvant therapy followed by interval debulking may be beneficial for selected patients with likely unresectable disease or unstable medical status.

Proper counseling of the patient with ovarian cancer is necessary to make appropriate decisions with respect to ovarian and uterine preservation in early disease, aggressive debulking surgery in advanced disease, and surgical palliation in recurrent chemotherapy-resistant disease.

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initial evaluation of patients with apparently confined ovarian cancer is incomplete due to inadequate staging. One retrospective analysis of the adequacy of staging in approximately 300 women with ovarian cancer showed that in cases in which surgery was performed by a general surgeon, 65% were inadequately staged. In cases in which surgery was performed by a gynecologist, 50% were inadequately staged. However, in cases in which surgery was performed by a gynecologic oncologist, only 3% were inadequately staged.[10] Recently, Munoz and colleagues reviewed the pattern of care received by women with epithelial ovarian cancer in the United States and concluded that of the women in whom presumed early ovarian cancer was diagnosed, only 10% received an appropriate diagnostic work-up, while the remaining 90% did not receive histopathologic confirmation or lymph node dissection.[11]

Surgical options

In virtually every patient with early stage ovarian cancer, initial surgical exploration is prompted by radiographic evidence of an adnexal mass in which malignancy may be suspected. Surgical exploration is performed first to determine the diagnosis, then to evaluate the extent of the disease and remove tumors. Many clinicians approach a solitary ovarian mass laparoscopically in the absence of suspicious radiographic findings and an elevated CA-125 level. A retrospective analysis of premenopausal as well as postmenopausal patients with ovarian masses that radiographically do not suggest malignancy indicates that only a very small percentage of such masses are actually malignant.[12] Thus an initial laparoscopic approach is justifiable.[13,14] However, laparoscopic drainage of an ovarian cyst that may be malignant is never justifiable because the extremely high recurrence rate and the risk of tumor dissemination are well known.[15] Although some studies have indicated that intraoperative rupture of ovarian malignancies may not affect survival,[14] other retrospective studies indicate that tumor spill may lead to early recurrence.[16] Recurrence at the laparoscopic port sites occurs more frequently in the presence of pre-existing peritoneal carcinomatosis or positive peritoneal cytology,[17] but it has been reported after intraoperative rupture of an otherwise confined ovarian cancer. Thus laparoscopic excision of suspicious, potentially malignant masses is not recommended.

Once ovarian cancer has been confirmed from a surgical specimen, the surgical options are removing the uterus and the contralateral adnexa, even in the absence of obvious tumor involvement, or sparing these organs with the intent of preserving fertility.[18] Because early ovarian cancer is often diagnosed in younger patients, fertility-preserving surgery is preferable. Occult metastases to pelvic organs is possible and needs to be considered, but recent studies indicate that the uninvolved ovary and the uterus may be safely preserved. One recent study reported that occult metastasis to the contralateral ovary in patients with apparent stage Ia or Ic disease who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy was found in only 2.5% of the cases.[19] Furthermore, clinical retrospective studies suggest that removal of apparently uninvolved reproductive organs may not be necessary.[20] For example, conservative surgery performed on 56 women with ovarian cancer resulted in survival comparable to that of 295 women with ovarian cancer on whom total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed.[9]

The management of the contralateral ovary and the uterus after childbearing is completed remains a matter of debate. Theoretically, patients are at high risk for a recurrence or even a second malignancy in the opposite ovary. Removal of that ovary after childbearing is completed may therefore be recommended. Moreover, women who have had ovarian cancer have an increased risk of endometrial cancer. Removal of the uterus would simplify the administration of hormone replacement therapy, eliminating the need for progestins.

Surgical staging

Regardless of the decision to remove or spare the uterus and contralateral adnexa, the surgical procedure is completed with surgical staging, accomplished by: systemic exploration of the abdomen and pelvis; washings of the pelvis, paracolic gutters and diaphragmatic recesses; biopsies of all adhesions and suspicious areas or of multiple random peritoneal areas from the bladder, pelvic side walls, cul-de-sac, gutters, and diaphragms in the absence of obvious lesions; an infracolic omentectomy; and dissection of the pelvic and aortic lymph nodes.[21,22] If a hysterectomy is not performed, an endometrial biopsy should be obtained.[22]

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Appendectomy is not currently recommended as part of the routine staging procedure, except in cases of mucinous tumors.[23] Staging by laparoscopy is generally comparable to staging by laparotomy and may be performed safely after laparoscopic removal of the affected adnexa or offered to a patient as a second procedure.[24,25]

The extent of lymph node dissection in apparently early ovarian cancer is still a matter of debate. Complete or radical node dissection of pelvic and aortic lymph nodes may not necessarily be beneficial and more limited dissection might be adequate.[26] Pathologic studies analyzing the distribution of lymph node metastases in early ovarian cancer are important guides for selective dissection. Earlier studies had indicated that aortic lymph nodes are involved even more frequently than pelvic nodes in advanced states of metastatic ovarian cancer.[27,28] Recent studies indicate that this is also true in early ovarian cancer, possibly reflecting preferential lymphatic spread along the gonadal vessels. In fact, the primary site of involvement in early stage disease may be the aortic nodes, particularly those located proximal to the inferior mesenteric artery.[30] Surgical staging should therefore include thorough aortic node sampling above the origin of the inferior mesenteric artery.[29,30] Another important and unsettled issue is the need for bilateral node sampling in cases of an apparently unilateral tumor. From observations that in apparently unilateral ovarian cancers, the incidence of contralateral pelvic or aortic lymph node involvement may be negligible,[31] many clinicians have adopted ipsilateral lymph node dissection as an adequate staging procedure. The Gynecologic Oncology Group (GOG) has even endorsed this pattern of practice in an ongoing protocol for early stage ovarian cancer (GOG protocol 175). Nevertheless, anecdotal observations indicate that contralateral node involvement is possible in the absence of ipsilateral node metastasis.[32] Therefore, such a conservative approach should be undertaken with caution until large-scale studies provide more information on this critical issue.

ADVANCED OVARIAN CANCER

Primary surgical treatment

Nearly 70% of patients with ovarian cancer present with advanced disease. Presenting symptoms include loss of appetite, abdominal bloating, and abdominal pain. An abdominal or pelvic mass and ascites may be appreciated on exam. Most patients will have disease spread within the peritoneal cavity, while some patients will also display disease in the chest, usually in the form of a malignant pleural effusion. In rare cases, liver parenchymal nodules, distant lymph node (eg, inguinal or scalene) metastasis, or distant parenchymal (eg, brain) metastasis may be encountered. Although imaging studies, including computed tomography and nuclear magnetic resonance, have proven helpful in the management of these patients, they may provide limited information in the differential diagnosis of pelvic tumors and often have a more limited use in establishing the amenability of the tumors to surgical resection.[33,34] The patient with evidence of a pelvic mass, omental tumor, peritoneal thickening, or ascites is likely to have advanced ovarian cancer, which poses specific clinical and surgical management issues. The diagnosis must be confirmed and the indications for surgical cytoreduction, the extent of cytoreduction, and the timing of the cytoreduction in relation to chemotherapy must be established.

Diagnosis

Surgical exploration remains the cornerstone for the diagnosis and immediate management of most patients with suspected ovarian cancer. Although the diagnosis of ovarian cancer may be suggested by abdominal and pelvic imaging and supported by positive peritoneal cytology from paracentesis, the sensitivities and specificities of the above methodologies, even when combined, are often disappointing.[33,34] Imaging studies may not distinguish accurately among a malignant ovarian mass, an ovarian tumor of low malignant potential, a benign adnexal mass, and a uterine mass. Furthermore, large stage I cystic tumors may be misinterpreted as ascites. Peritoneal cytology may be negative in stage III ovarian cancer.[35] As well, epithelial ovarian cancer may not be distinguishable from other intraperitoneal malignant or benign conditions on the basis of cytology alone.[36,37] Surgical exploration provides the opportunity for thorough palpation and visualization of the entire abdomen, as well as evaluation and removal of the mass for expedited histopathologic diagnosis. This information is critical for planning the appropriate surgical and postoperative management of the patient.

Rationale for surgical cytoreduction

Cytoreduction has proven to be beneficial in ovarian cancer. Largely supported by retrospective clinical evidence analyzing the effects of optimal cytoreduction, the practice of primary cytoreduction is also based on our current interpretations of the kinetics of solid tumor growth, the mechanism of action of chemotherapy, and the mechanisms underlying the spontaneous development of chemotherapy-resistant cell clones. Tumor growth is thought to follow the Gompertzian model, in which the rate of cells replicating at any given time correlates inversely with the volume of the tumor, such that a maximum number of tumor cells enters the replicative cycle when tumor volume is minimal. When tumor nodules outgrow their vascular supply, progressively larger numbers of tumor cells exit the replicative cycle and, as a result, become insensitive to a variety of cytotoxic agents.[38] Another theory suggests that cytotoxic agents kill a constant fraction rather than a constant number of tumor cells, regardless of the initial cell population. According to this model, cytotoxic chemotherapy is more efficacious on tumors of small volumes.[39] This implies exponential growth tumor kinetics, which may not be true for ovarian cancer. However, this model explains the observed benefit drawn from maximal cytoreductive efforts. In addition, the mathematical model of Goldie and Coldman predicts that spontaneous mutations which generate drug-resistant phenotypes occur randomly in tumor cells and that their frequency relates to the absolute number of tumor cells.[40] Therefore, the likelihood of chemotherapy-resistant clones increases in relation to residual tumor volume, and as a result, maximal cytoreduction would decrease the incidence of chemotherapy resistance in residual disease. Furthermore, additional benefit from cytoreduction may be derived from the decreased immunosuppressive effects of the tumor. Ovarian cancer produces large amounts of immunosuppressive cytokines, including interleukin-10, transforming growth factor-beta, and vascular-endothelial growth factor, that can suppress the activity of specific immune cell populations.[41,42] Tumor removal may improve immune effector function.

In practice, cytoreduction may decrease the number of chemotherapy cycles required to achieve clinical remission. Additional benefits derived from primary cytoreduction are improved gastrointestinal function, enhanced performance status, and better quality of life resulting from the removal of large intra-abdominal masses as well as ascites.[43] These benefits must be balanced against the potential risks and complications of cytoreductive surgery as well as against the potentially prolonged recovery time. The clinician must use judgment in individualizing the management of the patient with potential ovarian cancer, weighing the above considerations and the medical conditions of the patient.

Rationale for maximal cytoreduction

The criteria used to define optimal cytoreduction on the basis of residual disease have varied among studies. Difficulty interpreting results is also caused by the lack of accepted methods for reporting the actual total volume of residual disease rather than the diameters of individual tumor nodules; in many instances, numerous subcentimeter nodules seeding the visceral and parietal peritoneum are left behind, even in patients considered optimally debulked. These differences notwithstanding, most retrospective literature of the past 20 years has indicated a clear benefit of maximal cytoreduction.

The first systematic analysis of the effect of surgical debulking on the outcome of ovarian cancer reported that patients with no residual tumor had a median survival of 39 months compared with 12.7 months' median survival for patients with residual tumor of greater than 1.5 cm in maximum diameter.[44] Most studies have employed a diameter maximum of 0.5 cm, 1 cm, or 2 cm of residual disease to indicate optimal cytoreduction. On the basis of this classification, several reports have indicated that optimal debulking is associated with higher rates of complete pathologic response to chemotherapy, assessed by second-look laparotomy, and remarkably longer median survival of patients treated with platinum-based or, in earlier studies, non-platinum combination regimens.[45-57] The extent of residual disease emerged as an important factor affecting the outcome of ovarian cancer in a seminal retrospective review of GOG studies of optimal cytoreduction (defined as residual disease of less than 1 cm in GOG Protocol 52) and suboptimal cytoreduction (defined as residual disease of more than 1 cm in GOG Protocol 97). This review demonstrated that survival was inversely proportional to the

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diameter of maximum residual disease.[58] When patients underwent suboptimal cytoreduction and then received either standard-dose or high-dose chemotherapy with platinum/cyclophosphamide, patients with residual disease of 1–2 cm had better survival than patients with disease greater than 2 cm. Furthermore, in patients with optimally debulked ovarian cancer who then received either a platinum/cyclophosphamide or platinum/cyclophosphamide/doxorubicin combination, the 4-year survivals were 58% for patients with microscopic disease, 34% for patients with residual disease less than 2 cm, and 16% for patients with residual disease greater than 2 cm. Although an inverse correlation between residual tumor and survival has been widely reported, many of the studies have indicated that aggressive cytoreduction that does not reduce residual tumor to less than 2 cm did not result in improved survival. These results, along with the possible prolonged recovery and complications from radical cytoreductive surgery, call for a careful selection of patients in which maximal cytoreduction should be attempted.

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Although individual skill and approaches may vary among gynecologic oncology surgeons, tumor location may preclude surgical debulking in certain cases. Those patients might be best served with primary neoadjuvant chemotherapy, then interval debulking as outlined below.

Stage IV epithelial ovarian cancer is associated with a dismal outcome—the 5-year survival is much less than that for stage III patients. However, in more than half of these patients, malignant pleural effusion is the only evidence of extraperitoneal disease. Several recent reports indicate that these patients receive the same benefits from optimal cytoreduction as stage III patients.[52,59-61] Approximately 30–45% of patients with stage IV ovarian cancer are suited for optimal cytoreduction. In a report from the University of Pennsylvania, where 47 consecutive patients with stage IV epithelial ovarian cancer were analyzed, 26 patients (55%) were deemed stage IV on the basis of positive pleural effusion only, while the other 21 patients (45%) had intraperitoneal liver or metastatic disease outside the abdomen. Optimal cytoreduction was achieved in only 30% of the patients at the time of their staging procedure. The median survival of the suboptimal cytoreduction group was 17 months while the median survival in the optimal cytoreduction group was 37 months (P=0.0295).[61] Optimal cytoreduction may also be attempted in selected patients with both stage IV epithelial ovarian cancer and parenchymal hepatic metastases, but perioperative mortality may be as high as 20%.[52]

The effect of surgical cytoreduction has been widely documented in retrospective studies but never demonstrated through prospective trials. Some authorities have therefore recommended interpreting clinical findings with caution, arguing that the apparent benefits of optimal cytoreduction may in part reflect the differences in the underlying biology of selected tumors.[45] The question of whether biology or surgery causes the better outcome will likely remain unanswered, because appropriate prospective randomized studies of aggressive surgery vs less aggressive surgery (such as GOG protocol 80) have thus far failed to secure the necessary number of patients, due to patients' and physicians' biases. However, indirect evidence that aggressive surgery still influences the outcome of the disease is provided by retrospective analyses of survival of patients with advanced poor-prognosis disease who undergo optimal cytoreduction. In fact, resection of hepatic metastases or radical pelvic en bloc debulking with colorectal resection, resulting in optimal cytoreduction, is associated with prolongation of survival in many reports.[52,59,60,62]

Timing of cytoreduction

Optimal cytoreduction at the time of diagnosis varies among centers should be achievable by experienced gynecologic oncologists in at least 50% of patients, though the actual percentage varies among centers. Patients in whom optimal cytoreduction cannot be achieved during the primary operation may be offered interval debulking surgery, ie, a second attempt at optimal cytoreduction after three cycles of chemotherapy. Results from a study by the European Organization for the Research and Treatment of Cancer demonstrated that patients who underwent interval debulking had a median survival of 26 months compared with a median survival of 20 months for those who did not (P=0.012). In a large proportion of patients studied, optimal cytoreduction was achieved in interval debulking, and the overall survival of these patients did not differ from that of patients who received optimal cytoreduction during primary

surgery.[57] These reports have prompted some clinicians to advocate neoadjuvant chemotherapy followed by interval cytoreduction as the preferred approach to the management of ovarian cancer. However, when the rationale for performing exploration is considered, individual treatment decisions must be made on the basis of careful evaluation of the potential risks and benefits of surgical exploration and aggressive cytoreduction.[63,64] Studies have tried to identify clinical and radiographic parameters that might predict the amenability of tumors to optimal cytoreduction. The predictive power of these parameters, however, has not been satisfactory to date, and new algorithms are being developed.[65] Surgical exploration remains the ultimate means by which the resectability of a tumor can be assessed.

Surgical approach

Preoperative evaluation of the patient with suspected ovarian cancer should be thorough and include: a routine blood count; a biochemical profile with electrolytes, liver function tests, renal function tests, coagulation tests, and nutritional assessment; a chest radiograph; and an electrocardiogram. Imaging studies of the abdomen are also important. The presence of large amounts of ascites may indicate the need for placement of a central venous catheter and invasive cardiovascular perioperative monitoring. Identification of upper abdominal or retroperitoneal masses will guide intraoperative manual exploration of the abdomen. Evidence of partial or complete bowel obstruction warrants gastrointestinal work-up with imaging studies or endoscopy to rule out a gastrointestinal tumor and help in the formulation of a surgical plan.

The abdomen should be approached with a vertical incision extending from the pubic symphysis to the epigastrium to allow for thorough evaluation of the upper abdomen. Ascites should be drained and the abdomen should be explored for the presence of disease. Surgical exploration aims to identify the origin of the tumor, assess the extent of the disease, and estimate the likelihood of achieving optimal cytoreduction. Extensive tumor within the liver parenchyma, the celiac vessels, the porta hepatis, the mesentery of the small bowel, or the pelvic side walls may render optimal debulking unfeasible, making a patient eligible for neoadjuvant chemotherapy followed by interval cytoreduction. Furthermore, the resectability of upper abdominal masses, including diaphragmatic tumor, must be assessed at this time to decide the operative strategy.[21,66,67]

The omentum often harbors a cake-like tumor, which frequently involves the infracolic omentum, or more rarely, the gastrocolic omentum, but usually does not invade the muscularis of the transverse colon. A transverse colonic resection followed by a functional end-to-end anastomosis may be performed rapidly and safely to remove omental tumors, but this removal can often be adequately accomplished by an infracolic or a gastrocolic omentectomy. Resection of the transverse colon may be avoided if the wall of the bowel is not invaded by tumor. In fact, careful dissection can separate the transverse colon from the tumor while maintaining the integrity of the bowel. Extra care must be taken to avoid injury to the mesentery in this stage of the operation. Although the omental tumor often extends towards the spleen, removal of the spleen is rarely necessary to achieve optimal debulking.[68] Extra care needs to be taken to avoid injury to the splenic vessels or the splenic capsule while debulking tumor in proximity of these structures. Occasionally, tumor nodules appear to involve the surface of the liver. These nodules are generally superficial and can be resected safely to achieve optimal cytoreduction. Imaging studies provide valuable information and may support the decision to resect superficial hepatic tumors in the absence of other intraparenchymal metastatic lesions. Tumor involving the diaphragm may become the limiting factor in achieving optimal cytoreduction. Confluent sheets of fibrinous tumor, miliary coalescent nodules, or bulky tumor nodules may be present in this area. Several techniques have been proposed for the removal of such tumors, including diaphragmatic resection with primary repair of the diaphragm and placement of a chest tube, stripping of the peritoneum, and tumor resection using an ultrasonic aspirator or argon beam coagulator. The falciform ligament should be transected and the liver mobilized to give access to the diaphragmatic recess of the peritoneum. Tumor involving the small bowel may be resected if necessary by performing a limited bowel resection and an end-to-end functional anastomosis.[69,70] These procedures are especially valuable when small bowel involvement is the limiting factor in achieving optimal cytoreduction or when the bowel obstruction can be surgically

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relieved. Tumor involving the large bowel is usually present within the mesentery or adherent to the colonic serosa. Bowel resection may be avoided when the tumor does not invade the muscularis layer of the bowel, but when resection is necessary, it may be performed with an acceptable level of morbidity.[70,71]

Resection of the pelvic tumor often requires a radical retroperitoneal approach because the tumor often entirely distorts the anatomy of the pelvis and creates coalescent masses involving the dome of the bladder, the uterus, the adnexa, the rectum, and the distal sigmoid. In rare cases in which the lower sigmoid and rectum cannot be safely separated from the tumor, en bloc resection may be performed with a modified posterior approach. Retrospective studies indicate that optimal cytoreduction in patients about to undergo colorectal resection for ovarian cancer offers an important survival benefit.[62] The operation begins with proximal transection of the colon above the tumor, usually at the distal sigmoid. Resection proceeds posteriorly and laterally in the retroperitoneum, with ligation of the superior rectal vessels, progression into the presacral space, and then resection laterally into the pararectal space. The ureters are identified and the gonadal vessels ligated. Further dissection into the retroperitoneum continues laterally with identification of the uterine vessels. These may be ligated close to the uterus or, if access is hindered by the tumor, at a more proximal level as they branch out of the internal iliac or the superior vesical artery. A modified radical hysterectomy is then performed, with isolation of the ureter from the overlying parametrial tunnels. The uterovesical space can then be enhanced. Transection of the rectum can come before or after transection of the vagina, depending on the accessibility of the organs. Transecting the vagina first and then approaching the rectum from its anterior aspect may be preferable.

A colostomy is rarely required with cytoreduction because the integrity of the colorectal compartment can be safely restored in most cases, but preoperative bowel preparation is critical to the success of the anastomosis. Lower anterior colorectal anastomosis may be achieved either with the end-to-end anastomosis stapler or with hand-sewing. Resection of the rectum is not necessary when an adequate plane between the bowel and the tumor mass can be identified. In that case, radical peritoneal dissection may be limited to identification of the ureters, ligation of the gonadal and uterine vessels, and excision of the mass. In selected cases with no tumor involvement of the uterus, its removal may not be necessary to achieve optimal cytoreduction. However, removal of the uterus may offer advantages, such as simplification of hormone replacement therapy, better clinical appreciation of pelvic masses during the course of the disease, diagnosis of synchronous endometrial cancer, and prevention of metachronous tumors. Although microscopic involvement of retroperitoneal lymph nodes is routinely found in patients with advanced ovarian cancer, extensive lymph node dissection in the absence of bulky retroperitoneal disease does not offer any advantage to these patients.

Radical surgical debulking requires seasoned surgical skills and clinical judgment. A retrospective study revealed that trained gynecologic oncologists were 2.8 times more likely to achieve optimal cytoreduction (residual disease <1 cm) than other surgical specialists (81.7% vs 29.2%).[72] Increasing experience in the surgical management of these patients and advancements in perioperative critical care medicine, with improved cardiovascular monitoring and parental hyperalimentation, have notably decreased perioperative morbidity. Radical cytoreduction involving bowel surgery may be performed safely, with postoperative pneumonia as the most commonly encountered complication.[54,73] Other reported complications are: intraoperative or postoperative hemorrhage; coagulopathy; deep vein thrombosis and pulmonary embolism; pneumothorax; cerebrovascular accident; infection; congestive heart failure; myocardial ischemia; pulmonary edema; leak of intestinal anastomosis; genitourinary fistula; small bowel obstruction; renal failure; and lymphocele formation.

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SECOND-LINE SURGERY

The most commonly employed second-line operations for ovarian cancer are second-look laparotomies and laparoscopies that assess the pathologic response to chemotherapy in patients who display complete clinical response, and secondary cytoreductive surgery performed at the time of relapse in anticipation of further chemotherapy. Selected patients with advanced refractory disease may be eligible for palliative procedures performed on the gastrointestinal tract.

Second-look procedures

Second-look laparotomy was introduced in the 1960s as a means of evaluating the need for further chemotherapy in patients who achieved remission after treatment with alkylating agents such as melphalan.[74,75] Reports of chemotherapy-induced leukemia provided further motivation to reduce the length of chemotherapy in patients with complete clinical response. With the introduction of platinum-based combination chemotherapy, the rationale for performing second-look operations was increasingly challenged on the basis of the following considerations. First, the overall response rate of advanced ovarian cancer cases greatly increased. Second, the number of patients relapsing after a complete pathologic response to platinum-based chemotherapy was disappointingly high.[76,77] Finally, the incidence of chemotherapy-induced leukemia after platinum-based chemotherapy greatly decreased compared with that after treatment with alkylating agents. However, second-look procedures still find applications, especially within experimental protocols. The complication rate for second-look procedures is surprisingly low, with wound infection, urinary tract infection, and adynamic ileus being the complications most frequently reported. Second-look operations are not justified in patients at low risk for disease recurrence.[78]

Tremendous experience with laparoscopic second-look operations has been gained over the past decade, and recent reports indicate that the procedure can be completed in most patients with minimal complications,[79] although the reliability of the procedure varies with the ability of the physician.[79,80] The abdomen and pelvis are thoroughly explored after all adhesions are lysed. Biopsies of all suspicious areas should be submitted for expedited histopathologic diagnosis. Any tumors should be resected; in the absence of an obvious tumor, random peritoneal biopsies and washings should be performed. Residual aortic and pelvic lymph nodes should be resected at this time. Any remainders of the infundibulopelvic pedicles (gonadal vessels) should be resected. Traditionally, a second-look laparotomy includes a total abdominal hysterectomy.

Secondary cytoreductive surgery

Secondary cytoreductive surgery may be performed at the time of a second-look laparotomy if a bulky tumor is encountered in the absence of radiographic findings. Reports indicate that cytoreduction to a microscopic residual level of disease, when performed at the time of second-look laparotomy, results in an increased survival. Because such patients have been proven to harbor chemotherapy-resistant clones, second-line chemotherapy will need to be instituted.[81]

Secondary cytoreductive surgery may be performed in selected patients at the time of disease recurrence, in preparation for further chemotherapy. Patients with apparently resectable disease and a reasonably high likelihood of harboring chemotherapy-sensitive disease may be candidates for this approach. Although imaging studies may fail to reliably predict the patients in which optimal cytoreduction may be completed successfully, the presence of multiple bulky tumor nodules or the presence of bulky tumor in sanctuary areas such as the liver parenchyma, porta hepatis, celiac vessels, bowel mesentery, and pelvic side wall suggests that the tumor is probably unresectable, contraindicating a surgical approach. In selected cases, a laparoscopy before the cytoreductive surgery may be offered to determine the resectability of the disease. The presence of miliary intraperitoneal disease should also discourage further debulking attempts. The length of the disease-free interval is an important para-meter to be considered when deciding whether to proceed with cytoreduction. In fact, reports indicate that the length of the disease-free interval after induction cisplatin/paclitaxel chemotherapy may predict the tumor's response to repeated platinum-based chemotherapy as well the patient's overall survival. Patients with a prolonged disease-free interval show not only increased chemosensitivity but also an increased likelihood of achieving complete resection after secondary cytoreductive surgery.

The surgical principles of secondary debulking are identical to those that apply to primary operations. Just as with primary cytoreductive surgery, the extent of residual tumor after secondary cytoreductive surgery appears to affect the outcome of the disease. Retrospective analyses have indicated that patients in whom secondary debulking is performed to a microscopic level of residual disease show remarkably longer survival.[82] However, as with primary cytoreductive surgery, whether the secondary debulking itself has a therapeutic effect or whether the patients in whom the procedure is successful are those who have more indolent disease is difficult to establish.

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"Issues that must be thoroughly discussed with the patient include the preservation of fertility through conservative procedures, the aggressiveness of cytoreductive surgery, the undertaking of a second-look or a secondary debulking operation, and the attempt at palliative surgery."

Palliative surgery

Palliative surgery may be appropriate for selected patients with advanced refractory ovarian cancer and likely gastrointestinal complications,[83-85] such as gastric outlet obstruction, proximal or distal small bowel obstruction, or large bowel obstruction. Usually a patient with intestinal obstruction has a poor prognosis; few patients will survive more than a few months from the onset of obstruction. Nevertheless, some patients could potentially achieve a reasonable quality of life after the gastrointestinal complication is resolved. These patients may be eligible for palliative procedures that bypass or relieve the obstruction. However, careful preoperative patient selection is critical because most of these patients are severely debilitated, have a severely compromised bone marrow reserve from long courses of chemotherapy, may have platinum-induced compromised renal function, and may have undergone several abdominal surgeries. Gastric outlet obstruction carries the poorest prognosis because it is often associated with diffuse peritoneal carcinomatosis or bulky upper abdominal disease, which cannot be resected due to its proximity to the liver hilum or the celiac vessels. A gastric tube placed endoscopically or under radiographic guidance may be offered to these patients; it could also be placed intraoperatively in those patients in whom bulky unresectable upper abdominal disease is unexpectedly found during exploration. Small bowel obstructions can be managed surgically with a resection or a bypass procedure, depending on the resectability of the tumor. Tumor-free areas of the proximal bowel and the distal bowel, typically the ascending or transverse colon, must be identified to accomplish anastomosis with reasonable safety. Colonic obstructions may be managed with a diverting or loop colostomy, depending on the location and degree of obstruction as well as the amount and location of tumor-free bowel that is available for reconstruction. In extreme cases, a large bowel obstruction may be managed with a tube cecostomy. Parenteral hyperalimentation may be undertaken perioperatively to restore the nutritional status of the patient and allow recovery of the gastrointestinal function.

The decision to undertake such heroic measures necessitates careful evaluation of the patient's medical status and wishes because serious morbidity and even mortality may ensue. Quality time at home and feedings with a gastric tube may be more appropriate for some patients than hospitalization and extensive surgery. For patients who underwent surgery but could not have intestinal continuity reestablished, survival did not exceed 3 months, while for patients who received palliative surgery that achieved diversion, survival ranged from 2 to 7 months.[86] Literature reports of mortality rate during surgery are as high as 18% and the mean complication rate reported is 32%. Severe postoperative complications, such as intestinal fistulas and anastomotic leaks, can develop in a large proportion of patients.

CONCLUSIONS

Surgical management remains the cornerstone of therapy for ovarian cancer to date. This disease poses tremendous challenges to surgeons and other physicians, and its management requires their extensive training, surgical skill, and clinical judgment, as well as extensive preoperative counseling of the patient. The latter is particularly important because decisions related to the extent of the surgery should be made by the patient. Issues that must be thoroughly discussed with the patient include the preservation of fertility through conservative procedures, the aggressiveness of cytoreductive surgery, the undertaking of a second-look or a secondary debulking operation, and the attempt at palliative surgery. Available options need to be presented in detail, and benefits and risks discussed on an individual basis, thus enabling the patient to make critical decisions that will affect her overall prognosis and quality of life. OS

REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin.* 1998;48:6-29.
2. Coukos G, Rubin SC. Chemotherapy resistance in ovarian cancer: new molecular perspectives. *Obstet Gynecol.* 1998;91:783-792.
3. Taylor KJ, Schwartz PE. Screening for early ovarian cancer. *Radiology.* 1994;192:1-10.
4. Rosenthal A, Jacobs I. Ovarian cancer screening. *Semin Oncol.* 1998;25:315-325.
5. Einhorn N, Sjovall K, Knapp RC, et al. Prospective evaluation of serum CA-125 levels for early detection of ovarian cancer. *Obstet Gynecol.* 1992;80:14-18.
6. Rubin SC. Surgery for ovarian cancer. *Hematol Oncol Clin North Am.* 1992;6:851-865.
7. Buchsbaum HJ, Brady MF, Delgado G, et al. Surgical staging of carcinoma of the ovaries. *Surg Gynecol Obstet.* 1989;169:226-232.
8. Le T, Krepart GV, Lotocki RJ, Heywood MS. Clinically apparent early stage invasive epithelial ovarian carcinoma: should all be treated similarly? *Gynecol Oncol.* 1999;74:252-254.

9. Zanetta G, Rota S, Chiari S, et al. The accuracy of staging: an important prognostic determinator in stage I ovarian carcinoma. A multivariate analysis. *Ann Oncol.* 1998;9:1097-1101.
10. McGowan L, Lesher LP, Norris HJ, Barnett M. Misstaging of ovarian cancer. Obstet Gynecol. 1985;65:568-572.
11. Munoz KA, Harlan LC, Trimble EL. Patterns of care for women with ovarian cancer in the United States. *J Clin Oncol.* 1997;15:3408-3415.
12. DePriest PD, Gallion HH, Pavlik EJ, Kryscio RJ, van Nagell JR. Transvaginal sonography as a screening method for the detection of early ovarian cancer. *Gynecol Oncol.* 1997;65:408-414.
13. Dottino PR, Levine DA, Ripley DL, Cohen CJ. Laparoscopic management of adnexal masses in premenopausal and postmenopausal women. *Obstet Gynecol.* 1999;93:223-228.
14. Mettler L, Semm K, Shive K. Endoscopic management of adnexal masses. *J Soc Laparoendosc Surg.* 1997;1:103-12.
15. Marana R, Caruana P, Muzii L, Catalano GF, Mancuso S. Operative laparoscopy for ovarian cysts. Excision vs. aspiration. *J Reprod Med.* 1996;41:435-488.
16. Leminen A, Lehtovirta P. Spread of ovarian cancer after laparoscopic surgery: report of eight cases. *Gynecol Oncol.* 1999;75:387-390.
17. Wang PH, Yuan CC, Lin G, Ng HT, Chao HT. Risk factors contributing to early occurrence of port site metastases of laparoscopic surgery for malignancy. *Gynecol Oncol.* 1999;72:38-44.
18. Benjamin I, Rubin SC. Management of early-stage epithelial ovarian cancer. *Obstet Gynecol Clin North Am.* 1994;21:107-119.
19. Benjamin I, Morgan MA, Rubin SC. Occult bilateral involvement in stage I epithelial ovarian cancer. *Gynecol Oncol.* 1999;72:288-191.
20. McHale MT, DiSaia PJ. Fertility-sparing treatment of patients with ovarian cancer. *Compr Ther.* 1999;25:144-150.
21. Hoskins W, Rice L, Rubin S. Ovarian cancer surgical practice guidelines. Society of Surgical Oncology practice guidelines. *Oncology (Huntingt).* 1997;11: 896-900, 903-904.
22. Gynecologic Oncology Group. Ovarian cancer surgical procedures. *In Surgical Manual* 1999:10-12.
23. Bese T, Kosebay D, Kaleli S, Oz AU, Demirkiran F, Gezer A. Appendectomy in the surgical staging of ovarian carcinoma. *Int J Gynaecol Obstet.* 1996;53:249-252.
24. Possover M, Krause N, Plaul K, Kuhne-Heid R, Schneider A. Laparoscopic para-aortic and pelvic lymphadenectomy: experience with 150 patients and review of the literature. *Gynecol Oncol.* 1998;71:19-28.
25. Childers JM, Lang J, Surwit EA, Hatch KD. Laparoscopic surgical staging of ovarian cancer. *Gynecol Oncol.* 1995;59:25-33.
26. Hacker NF. Systematic pelvic and paraaortic lymphadenectomy for advanced ovarian cancer—therapeutic advance or surgical folly? *Gynecol Oncol.* 1995;56:325-7.
27. Chen SS, Lee L. Incidence of para-aortic and pelvic lymph node metastases in epithelial carcinoma of the ovary. *Gynecol Oncol.* 1983;16:95-100.
28. Rose PG, Piver MS, Tsukada Y, Lau TS. Metastatic patterns in histologic variants of ovarian cancer. An autopsy study. *Cancer.* 1989;64:1508-1513.
29. Onda T, Yoshikawa H, Yokota H, Yasugi T, Taketani Y. Assessment of metastases to aortic and pelvic lymph nodes in epithelial ovarian carcinoma. A proposal for essential sites for lymph node biopsy. *Cancer.* 1996;78:803-808.
30. Tsumura N, Sakuragi N, Hareyama H, et al. Distribution pattern and risk factors of pelvic and para-aortic lymph node metastasis in epithelial ovarian carcinoma. *Int J Cancer.* 1998;79:526-530.
31. Benedetti-Panici P, Greggi S, Maneschi F, et al. Anatomical and pathological study of retroperitoneal nodes in epithelial ovarian cancer. *Gynecol Oncol.* 1993;51:150-154.
32. Walter AJ, Magrina JF. Contralateral pelvic and aortic lymph node metastasis in clinical stage I epithelial ovarian cancer. *Gynecol Oncol.* 1999;74:128-129.
33. Forstner R, Hricak H, Occhipinti KA, Powell CB, Frankel SD, Stern JL. Ovarian cancer: staging with CT and MR imaging. *Radiology.* 1995;197:619-626.
34. Meyer JI, Kennedy AW, Friedman R, Ayoub A, Zepp RC. Ovarian carcinoma: value of CT in predicting success of debulking surgery. *AJR Am J Roentgenol.* 1995;165:875-878.
35. Rubin SC, Dulaney ED, Markman M, Hoskins WJ, Saigo PE, Lewis JL. Peritoneal cytology as an indicator of disease in patients with residual ovarian carcinoma. *Obstet Gynecol.* 1988;71:851-853.
36. Nunez C. Cytopathology and fine-needle aspiration in ovarian tumours: its utility in diagnosis and management. *Curr Top Pathol.* 1989;78:69-83.
37. Pisharodi LR, Bedrossian CW. Cytopathology of serous neoplasia of the ovary and the peritoneum: differential diagnosis from mesothelial proliferations. *Diagn Cytopathol.* 1996;15:292-295.
38. Skipper HE. Thoughts on cancer chemotherapy and combination modality therapy (1974). *JAMA.* 1974;230:1033-5.
39. Skipper H, Shabel FJ, Wilcox W. Experimental evaluation of potential anticancer agents. *Cancer Chemother Rep.* 1964;35:1-7.
40. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep.* 1979;63:1727-1733.
41. Merogi AJ, Marrogi AJ, Ramesh R, Robinson WR, Fermin CD, Freeman SM. Tumor-host interaction: analysis of cytokines, growth factors, and tumor-infiltrating lymphocytes in ovarian carcinomas. *Hum Pathol.* 1997;28:321-331.
42. Punnonen R, Teisala K, Kuoppala T, Bennett B, Punnonen J. Cytokine production profiles in the peritoneal fluids of patients with malignant or benign gynecologic tumors. *Cancer.* 1998;83:788-796.
43. Blythe JG, Wahl TP. Debulking surgery: does it increase the quality of survival? *Gynecol Oncol.* 1982;14:396-408.
44. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr.* 1975;42:101-104.
45. Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1992;47:159-166.
46. Ng LW, Rubin SC, Hoskins WJ, et al. Aggressive chemosurgical debulking in patients with advanced ovarian cancer. *Gynecol Oncol.* 1990;38:358-363.
47. Hoskins WJ, Rubin SC, Dulaney E, et al. Influence of secondary cytoreduction at the time of second-look laparotomy on the survival of patients with epithelial ovarian carcinoma. *Gynecol Oncol.* 1989;34:365-371.
48. Rubin SC, Randall TC, Armstrong KA, Chi DS, Hoskins WJ. Ten-year follow-up of ovarian cancer patients after second-look laparotomy with negative findings. *Obstet Gynecol.* 1999;93:21-24.
49. Lippman SM, Alberts DS, Slymen DJ, et al. Second-look laparotomy in epithelial ovarian carcinoma. Prognostic factors associated with survival duration. *Cancer.* 1988;61:2571-2577.
50. Podratz KC, Malkasian GD, Hilton JF, Harris EA, Gaffey TA. Second-look laparotomy in ovarian cancer: evaluation of pathologic variables. *Am J Obstet Gynecol.* 1985;152:230-238.

51. Gallup DG, Talledo OE, Dudzinski MR, Brown KW. Another look at the second-assessment procedure for ovarian epithelial carcinoma. *Am J Obstet Gynecol.* 1987;157:590-596.
52. Naik R, Nordin A, Cross PA, Hemming D, de Barros Lopes A, Monaghan JM. Optimal cytoreductive surgery is an independent prognostic indicator in stage IV epithelial ovarian cancer with hepatic metastases. *Gynecol Oncol.* 2000;78:171-175.
53. Pecorelli S, Odicino F, Favalli G. Ovarian cancer: best timing and applications of debulking surgery. *Ann Oncol* 2000;11 Suppl 3:141-144.
54. Lichtenegger W, Sehouli J, Buchmann E, Karajanev C, Weidemann H. Operative results after primary and secondary debulking-operations in advanced ovarian cancer (AOC). *J Obstet Gynaecol Res.* 1998;24:447-451.
55. Hoskins PJ, O'Reilly SE, Swenerton KD, Spinelli JJ, Fairey RN, Benedet JL. Ten-year outcome of patients with advanced epithelial ovarian carcinoma treated with cisplatin-based multimodality therapy. *J Clin Oncol.* 1992;10:1561-1568.
56. Weiser EB, Burke TW, Heller PB, Woodward J, Hoskins WJ, Park RC. Determinants of survival of patients with epithelial ovarian carcinoma following whole abdomen irradiation (WAR). *Gynecol Oncol.* 1988;30:201-208.
57. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med.* 1995;332:629-634.
58. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol.* 1994;170:974-9; discussion 979-980.
59. Curtin JP, Malik R, Venkatraman ES, Barakat RR, Hoskins WJ. Stage IV ovarian cancer: impact of surgical debulking. *Gynecol Oncol.* 1997;64:9-12.
60. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol.* 1999;72:278-287.
61. Liu PC, Benjamin I, Morgan MA, King SA, Mikuta JJ, Rubin SC. Effect of surgical debulking on survival in stage IV ovarian cancer. *Gynecol Oncol.* 1997;64:4-8.
62. Scarabelli C, Gallo A, Franceschi S, et al. Primary cytoreductive surgery with rectosigmoid colon resection for patients with advanced epithelial ovarian carcinoma. *Cancer.* 2000;88:389-397.
63. Hacker NF, van der Burg ME. Advanced ovarian cancer. Debulking and intervention surgery. *Ann Oncol.* 1993;4:17-22.
64. Vergote IB, De Wever I, Decloedt J, Tjalma W, Van Gramberen M, van Dam P. Neoadjuvant chemotherapy versus primary debulking surgery in advanced ovarian cancer. *Semin Oncol.* 2000;27:31-36.
65. Bristow RE, Duska LR, Lambrou NC, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. *Cancer.* 2000;89:1532-1540.
66. Randall TC, Rubin SC. Surgical management of ovarian cancer. *Semin Surg Oncol.* 1999;17:173-180.
67. Benjamin I, Rubin SC. Advances in cytoreductive surgery of gynecologic cancers. Cancer Treat Res. 1998;95:203-217.
68. Nicklin JL, Copeland LJ, O'Toole RV, Lewandowski GS, Vaccarello L, Havenar LP. Splenectomy as part of cytoreductive surgery for ovarian carcinoma. *Gynecol Oncol.* 1995;58:244-247.
69. Weber AM, Kennedy AW. The role of bowel resection in the primary surgical debulking of carcinoma of the ovary. *J Am Coll Surg.* 1994;179:465-470.
70. Tamussino KF, Lim PC, Webb MJ, Lee RA, Lesnick TG. Gastrointestinal surgery in patients with ovarian cancer. *Gynecol Oncol.* 2001;80:79-84.
71. Rubin SC, Benjamin I, Hoskins WJ, Pierce VK, Lewis JL. Intestinal surgery in gynecologic oncology. *Gynecol Oncol.* 1989;34:30-33.
72. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol.* 1992;47:203-209.
73. Chen SS, Bochner R. Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma. *Gynecol Oncol.* 1985;20:190-195.
74. Rubin SC. The value of second-look laparotomy in ovarian cancer. *Oncology (Huntingt).* 1987;1:45-51.
75. Rubin SC, Lewis JL. Second-look surgery in ovarian carcinoma. *Crit Rev Oncol Hematol.* 1988;8:75-91.
76. Rubin SC, Hoskins WJ, Hakes TB, Markman M, Cain JM, Lewis JL. Recurrence after negative second-look laparotomy for ovarian cancer: analysis of risk factors. *Am J Obstet Gynecol.* 1988;159:1094-1098.
77. Rubin SC, Hoskins WJ, Saigo PE, et al. Prognostic factors for recurrence following negative second-look laparotomy in ovarian cancer patients treated with platinum-based chemotherapy. *Gynecol Oncol.* 1991;42:137-141.
78. Rubin SC, Jones WB, Curtin JP, Barakat RR, Hakes TB, Hoskins WJ. Second-look laparotomy in stage I ovarian cancer following comprehensive surgical staging. *Obstet Gynecol.* 1993;82:139-42.
79. Husain A, Chi DS, Prasad M, et al. The role of laparoscopy in second-look evaluations for ovarian cancer. *Gynecol Oncol.* 2001;80:44-7.
80. Clough KB, Ladonne JM, Nos C, Renolleau C, Validire P, Durand JC. Second look for ovarian cancer: laparoscopy or Laparotomy? A prospective comparative study. *Gynecol Oncol.* 1999;72:411-7.
81. Morgan MA, Rubin SC. Secondary cytoreduction in epithelial ovarian cancer. *Crit Rev Oncol Hematol.* 1995;18:1-8.
82. Janicke F, Holscher M, Kuhn W, et al. Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. *Cancer.* 1992;70:2129-36.
83. Rubin SC. Intestinal obstruction in advanced ovarian cancer: what does the patient want? *Gynecol Oncol.* 1999;75:311-2.
84. Randall TC, Rubin SC. Management of intestinal obstruction in the patient with ovarian cancer. *Oncology (Huntingt).* 2000;14:1159-63; discussion 1167-8, 1171-5.
85. Rubin SC, Hoskins WJ, Benjamin I, Lewis JL. Palliative surgery for intestinal obstruction in advanced ovarian cancer. *Gynecol Oncol.* 1989;34:16-9.
86. Hoskins WJ, Chi DS, Boente MP, Rubin SC. State of the art surgical management of ovarian cancer. *Cancer Res. Ther Contr.* 1999;9:373-382.