The Role of Cytoreductive/Debulking Surgery in Ovarian Cancer

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Ovarian cancer, cytoreductive surgery

Abstract
Ovarian cancer is the fifth most common cause of cancer-related death among women in the United States, although the median survival of patients has been increasing over the past few decades. In patients with epithelial ovarian cancer, chemotherapy has increased survival. Platinum agents combined with taxanes have become standard treatment. Intraperitoneal chemotherapy has also increased survival. Cytoreductive surgery to optimally debulk a tumor or, ideally, remove any gross disease has also been shown to increase survival. Each 10% increase in cytoreduction correlates with a 5.5% increase in median survival. The ability to successfully perform optimal cytoreduction ranges from 20% to 90%. Many institutions have recently begun to perform aggressive/ultraradical procedures to achieve this result. Interval cytoreduction may also benefit patients whose initial surgery is suboptimal, especially if the first procedure was performed by a surgeon unfamiliar with the disease. Secondary cytoreduction can increase survival in patients with low-volume disease and a long disease-free interval. All of these procedures should be performed by a specialist trained in ovarian cancer surgery. (JNCCN 2008;6:803–811)

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Learning objectives
Upon completion of this activity, participants will be able to:
• Identify factors that predict outcomes of optimal cytoreduction
• Describe survival times associated with the use of cytoreduction surgery in ovarian cancer
• Define optimal cytoreduction according to the criterion of the Gynecologic Oncology Group
• Describe current first-line therapy for ovarian cancer
• Describe the mortality associated with ovarian cancer in the United States
• Define optimal cytoreduction according to the criterion of the Gynecologic Oncology Group

Among women in the United States, ovarian cancer is the eighth most common malignancy and the fifth most common cause of cancer-related death. An incidence of 21,650 cases and 15,520 deaths attributable to this disease are estimated in 2008.1 Unfortunately, 75% of ovarian cancers are diagnosed as stage III or IV.2 At the time of surgery, many patients have extensive disease throughout the abdominal cavity. The median survival in advanced-stage disease has greatly improved in the past 3 decades.3,4 The efficacy of chemotherapy has improved, with platinum combined with taxanes becoming standard treatment.5 Intraperitoneal chemotherapy for optimally
cytoreduced epithelial ovarian cancer has increased survival by 1.5 years.\(^3\)

Surgery has always played a major role in treatment of ovarian cancer, but many controversies exist. Although most experts agree that cytoreductive surgery improves survival, whether aggressive/ultraradical surgery (e.g., addition of hepatic resection, splenectomy, distal pancreatectomy, peritonectomy, modified posterior exenteration) increases survival in patients with extensive tumor is unknown. This article focuses on the role of cytoreductive/debulking surgery in epithelial ovarian cancers.

**Definition of Optimal Cytoreduction**

When members of the Society of Gynecologic Oncologists were asked what they consider optimal cytoreduction in stage IIIC epithelial ovarian cancers, 12% defined it as no residual disease; 13.7% as 0.5 cm or less residual disease; 60.8% as 1.0 cm or less; 8.7% as 2.0 cm or less; and 1.3% used other criteria.\(^a\) According to the Gynecologic Oncology Group (GOG), optimal cytoreduction is defined as the largest residual tumor nodule measuring 1 cm or less.\(^b\) This definition is the most widely accepted among gynecologic oncologists.

The fact that residual disease is determined by the operating surgeon has obvious pitfalls. Prefontaine et al.\(^c\) used a simulated patient model to evaluate surgeon accuracy in estimating tumor size. Most surgeons underestimated rather than overestimated tumor size; 25% of patients with suboptimal disease and 20% with optimal disease were erroneously categorized.

**Evidence Against Aggressive/Ultraradical Cytoreductive Surgery**

Some believe that tumor biology and its ability to respond to chemotherapy is more important than the type of surgery performed. Although most experts agree that survival is better with less residual disease present, the question remains whether aggressive/ultraradical surgery improves survival. Although surgery is becoming more radical in many institutions, the efficacy and variety of different chemotherapeutic agents have also increased. Platinum agents combined with taxanes are now standard treatment.\(^d\) Several different second-line agents are available for use, including topotecan, liposomal doxorubicin, gemcitabine, and bevacizumab.\(^e\,f\)

Most would agree that a smaller amount of tumor initially present at surgery is associated with increased survival. This does not necessarily mean that a patient with extensive disease who is cytoreduced to minimal disease will have the same outcome.

GOG protocol 52 compared patients with stage III ovarian cancer who initially had disease 1 cm or less with those who had larger disease at onset that was cytoreduced to 1 cm or less. The group with small-volume disease at the onset of surgery survived longer than patients who underwent cytoreduction. The authors concluded that bulky disease has a more aggressive tumor biology than small-volume disease.\(^g\)

The Scottish Randomized Trial in Ovarian Cancer-I (SCOTROC-1) study looked at the impact of cytoreductive surgery on progression-free survival (PFS). Optimal cytoreduction was associated with increased PFS, but mainly for patients with less-extensive disease at the onset of surgery. The authors concluded that tumor biology was a major determinant of PFS and that optimal surgery could not fully compensate for this. Although patients outside the United Kingdom were more likely to undergo optimal cytoreduction than those from within, PFS was not different in the groups after adjusting for presurgery prognostic factors.\(^h\)

In a microarray analysis of 44 advanced ovarian cancer specimens that were optimally and suboptimally cytoreduced, Berchuck et al.\(^i\) found different patterns of gene expression between the groups. This finding further supports the hypothesis that tumor biology may be different.\(^i\)

**Evidence for Aggressive/Ultraradical Cytoreductive Surgery**

Many theoretical reasons exist for performing aggressive cytoreduction of tumors. Larger tumors can have poorly vascularized areas, thus decreasing exposure to cytotoxic chemotherapy. These cells can also have a lower growth fraction. Cytoreduction can remove chemoresistant clonogenic cells, causing the smaller residual disease to have an increased growth fraction and making it more sensitive to chemotherapy. Reducing adverse metabolic consequences caused by
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this tumor may improve the physiologic status of patients, enabling them to eat better, among other functions. Tumor removal has also been hypothesized to enhance immune function.14,15

Meigs16 was the first to recommend that patients with ovarian cancer have as much tumor removed as possible. In 1975, Griffiths17 was the first to show that the size of residual disease correlated with survival. Since then, many studies have shown that aggressive cytoreduction increases survival when resulting in small or no gross residual disease.18–31

In an analysis of data from 6 major GOG trials, Wintett al.12 found that patients with any residual disease had an increased risk for death compared with those who had microscopic residual disease. In a study of 408 patients with stage IIIIC ovarian cancer, Eisenkop et al.18 showed that cytoreducing tumors to no visible disease influenced survival more significantly than the extent of metastatic disease present before surgery. These and many other studies have shown that optimal cytoreduction increases survival, but the goal should be no gross residual disease.

In a meta-analysis of 53 studies involving 6885 patients with stage III or IV ovarian cancer, Bristow et al.14 found that each 10% increase in cytoreduction correlated with a 5.5% increase in median survival time. Patients with a maximal cytoreductive effort of 25% or less had a median survival of 22.7 months compared with 33.9 months for patients with a greater than 75% maximal cytoreductive effort. More recent studies in this meta-analysis showed statistically significant longer median survival times than older studies.

A good prospective randomized trial on this subject will be difficult to develop. The GOG attempted this with protocol 80, which evaluated initial surgical debulking followed by chemotherapy versus chemotherapy followed by surgical debulking. However, this trial accrued only 2 patients and was closed after 2 years.35

The 2004 consensus statement on the management of ovarian cancer from the Third International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004) unanimously recommended up-front maximal surgical effort at cytoreduction with the goal of no residual disease.40

Patients with stage IV ovarian cancer (i.e., disease outside of the intraperitoneal cavity) also experience improved survival when undergoing aggressive cytoreductive surgery. Many studies mentioned previously included patients with stage IV disease. Optimal cytoreduction increased survival even in these patients. Among other studies examining the impact of cytoreductive surgery in patients with stage IV disease,12,20,22,34,37–47 most conclude that a large percentage of these patients can be optimally cytoreduced with increased survival.36–39

How Likely is Optimal Cytoreduction?

Although many studies have examined the benefits of cytoreduction, what is the chance of optimally cytoreducing a patient? Eisenkop et al.18 reported the highest optimal cytoreduction rates. Of 139 patients with stage IIIIC and IV ovarian cancer undergoing surgery, 85.3% had all visible tumor excised, 13.5% had 1 cm or less residual, and 1.2% had unresected bulky disease. Mean operative time was 254 minutes with a mean estimated blood loss of 1190 mL. The median hospital stay was 12 days, and morbidity and mortality were 41.7% and 1.8%, respectively.

Chi et al.41 reported on 465 patients with stage IIIIC epithelial ovarian cancer. No gross residual disease was achieved in 14.4%, less than 1 cm in 36.3%, and greater than 1 cm in 49.2%. The mean operative time was 194 minutes, mean estimated blood loss was 500 mL, and the average hospital stay was 10 days. Perioperative mortality was 0.6%.

In a report on patients with advanced epithelial ovarian cancer undergoing surgery from 1997 to 2006, a group at Johns Hopkins examined conventional criteria for predicting unresectable disease, including ascites greater than 1000 mL, carcinomatosis, splenic involvement greater than 1 cm, omental extension to the spleen, parenchymal liver disease, disease involving the porta hepatis, and bulky disease involving the diaphragm. The overall ability to achieve optimal debulking was 92.2%. Even patients with 5 high-risk factors still had an 80% ability to experience optimal debulking. Therefore, most patients can probably be optimally debulked when treated by the right surgeon in the right institution.42

In reviewing the literature, rates of optimal or complete cytoreduction range from 20% to 90%, with higher rates occurring more often when patients are managed by specialists trained in ultraradical/aggressive surgical methods. The tradeoff is increased morbidity.18–31,44,54,55
Do Predictors Exist for Optimal Cytoreduction?

The inability to predict patients who cannot be optimally cytoreduced is a dilemma for all gynecologic oncologists. CA-125s, PET scans, or CT findings of large volume ascites, carcinomatosis, and involvement of upper abdominal organs have all been examined as preoperative predictors for optimal cytoreduction. Unfortunately no test or imaging modality can reliably predict who can be optimally cytoreduced.\(^4,6,16-42\)

Elderly Patients and Surgery

Up-front surgery, especially aggressive debulking procedures, is not applicable to everyone with advanced ovarian malignancy. Many patients with ovarian cancer present in their 70s and 80s. A question that frequently arises is whether elderly patients should undergo surgery. Most studies on this issue conclude that age itself is not an independent risk factor of how patients will respond; comorbidities are more important. Survival in elderly patients has been shown to significantly increase if they can be optimally cytoreduced.\(^43-47\)

Therefore, which elderly patients can undergo surgery must be decided wisely. Some patients may be helped with up-front aggressive cytoreduction, but others may be better candidates for neoadjuvant chemotherapy before surgery.

Interval Cytoreductive/Debulking Surgery After Primary Suboptimal Surgery

Two major studies have looked at interval debulking after initial suboptimal cytoreduction followed by chemotherapy. The first trial was performed by the EORTC. The study group consisted of patients with ovarian cancer who underwent initial surgery but were suboptimally cytoreduced and subsequently underwent 3 cycles of cisplatin and cyclophosphamide chemotherapy. They were then randomized to interval cytoreduction followed by 3 more cycles of chemotherapy or chemotherapy only. The PFS and overall survival were significantly longer in the interval debulking group (\(P = .01\)). The median survival was 26 months of patients who underwent interval cytoreductive surgery and 20 months for those who did not. The risk of death decreased by 33% (\(P = .008\)) in the group undergoing interval surgery.\(^6\)

In the second study, GOG protocol 152 studied 424 patients who initially underwent suboptimal cytoreduction. Subjects were treated with 3 cycles of cisplatin and paclitaxel. Patients were randomized to 3 more cycles of chemotherapy versus interval cytoreductive surgery followed by chemotherapy. No difference was seen in PFS or overall survival. Median survival was 33.9 months in the interval-surgery group and 33.7 months in the chemotherapy-only group.\(^69\)

Many reasons have been postulated for the discrepancy between these studies. In the GOG study, most initial surgeries were performed by gynecologic oncologists (95%), and therefore most patients may have already had a maximal effort at cytoreduction, whereas in the EORTC trial, the surgical experience of those performing the initial operation was not defined and patients may not have undergone a maximal attempt at initial cytoreduction. Furthermore, the chemotherapy regimens differed in these trials. The earlier EORTC trial used cyclophosphamide, not paclitaxel, in addition to the cisplatin. The paclitaxel combination has been shown to result in superior survival compared with the cyclophosphamide regimen.\(^4\)

Bristow et al.\(^50\) reviewed 9 studies on interval cytoreduction. The authors concluded that interval cytoreduction after a concerted, but suboptimal, attempt at up-front cytoreduction does not increase survival. If initial suboptimal surgery is performed by a surgeon experienced in aggressive cytoreductive surgery, such as a gynecologic oncologist, interval cytoreduction will probably not help. If the initial procedure is not performed by a surgeon experienced in aggressive cytoreductive surgery, then interval cytoreduction may be beneficial.

Neoadjuvant Chemotherapy Followed by Interval Debulking

Neoadjuvant chemotherapy is defined as the administration of chemotherapy after histologic verification of ovarian cancer by biopsy only. Colombo et al.\(^75\) compared initial cytoreductive surgery with neoadjuvant chemotherapy followed by surgery in patients with stage III and IV disease. In the patients undergoing initial surgery, the 5-year survival was 50% for patients with no residual disease, 30% if residual disease was less
than 1 cm, and 14% if residual disease was greater than 1 cm. For patients undergoing neoadjuvant chemotherapy, overall survival with no residual disease after interval debulking was 30%. No patient survived 5 years if any gross disease remained at the interval surgery.

In a review of 26 studies addressing this topic, Bristow et al. concluded that most studies on neoadjuvant chemotherapy show a median survival time inferior to matched controls undergoing primary debulking surgery. Also, the median survival time was at best the same, but often inferior, compared with historical patients undergoing suboptimal primary surgery. The authors concluded that maximal primary cytoreductive surgery is the standard of care, and that neoadjuvant chemotherapy represents a management option for only a small number of patients.

A Cochrane review on this topic concluded there is no good evidence that neoadjuvant chemotherapy before debulking surgery, for women with advanced epithelial ovarian cancer, is superior to conventional debulking surgery and platinum-based chemotherapy.

### Secondary Cytoreduction/Debulking

Despite a greater than 70% response to initial therapy with platinum/taxane chemotherapy, the recurrence rate is also 70%. Therefore, most patients and physicians are faced with the question of whether surgery for recurrent ovarian cancer is an option.

Secondary cytoreduction is defined as cytoreductive surgery after initial treatment is completed. Munkarah and Coleman reviewed this topic in 2004, separating studies looking specifically at hepatic resection, because these patients may have a different tumor biology. In a review of 10 studies, 67% of patients were considered optimally cytoreduced, with optimal defined as ranging from 0.5 to 2 cm. All macroscopic disease was successfully resected in 41% of patients (range, 13%–82%). Major perioperative morbidity occurred in 11% of patients; perioperative mortality was 1.4%. Survival ranged from less than 8 to 25.1 months in the suboptimal groups, from 9 to 56.9 months for the optimal groups, and from 29 to 100 months in patients undergoing complete resection. The best candidates for secondary cytoreduction are those with longer recurrence-free intervals from their initial treatment and fewer recurrence sites. The authors concluded that these data suggest a benefit for secondary cytoreduction in recurrent ovarian cancer, and that patients with no remaining gross residual disease can survive an average of 44 to 60 months.

Many other articles have since been published on this topic. Median postrecurrence survivals ranged from 30 to 61 months in patients who were optimally debulked and 17 to 19 months if debulking was suboptimal. Salani et al. found 3 variables that predicted increased survival: diagnosis to recurrence interval greater than 18 months, complete cytoreduction at surgery, and only 1 or 2 recurrence sites on radiographic imaging before secondary debulking surgery.

Tertiary cytoreduction has also been studied. In a review of 47 patients undergoing tertiary cytoreduction, Karam et al. found that 64% of patients were successfully cytoreduced to microscopic disease. Overall survival was statistically longer in patients with microscopic disease versus those with macroscopic disease (24 vs. 16 months). The only predictor of poor survival was the presence of diffuse disease at surgery; 26% of patients had severe postoperative complications. The authors concluded that tertiary cytoreduction is associated with improved survival, and preoperative imaging may guide the selection of candidates for this surgery.

### Who Should Be Performing These Surgeries

The ability to optimally debulk patients with advanced ovarian cancer has been shown to be up to 98.8%. Gynecologic oncologists at high volume centers are best suited to do this. The GCIG OCCC 2004 unanimously recommended that surgery for these patients be performed by an appropriately trained surgeon experienced in the management of ovarian cancer.

Bristow et al. defined low-volume surgeons as those who handle 4 or fewer cases per year, intermediate-volume as 5 to 9 cases per year, and high-volume as 10 or more cases per year. Low-volume hospitals were defined as those handling 9 or fewer cases per year, intermediate-volume as 10 to 19 cases per year, and high-volume as 20 cases or more per year. The largest combined category in which patients received care was at low-volume hospitals with a low-volume surgeon, which accounted for 37%. High-volume hospitals with a high-volume surgeon only accounted for 14.4%.

In a review of 19 studies examining the relationship between care setting (type of gynecologist or...
hospital) and outcomes, Vernooij et al. found that gynecologic oncologists consistently performed more adequate staging and debulking. Surgery performed by a gynecologic oncologist resulted in a 5- to 8-month median survival benefit for patients with advanced disease.

Conclusions
Aggressive surgical cytoreduction for patients with ovarian cancer is becoming more common. When aggressive debulking is performed, median survival is increased. Unfortunately, these trials are not randomized. Trials involving surgery are difficult to interpret because of different skills among surgeons. Patients who have a better performance status and fewer comorbidities tend to undergo more aggressive surgery. Therefore, whether their survival improved because of a more aggressive cytoreductive procedure or from their overall better health is unclear.

Based on available data, aggressive surgical cytoreduction should be performed if possible. Most recent studies show an increase in median survival. Also, if more patients are optimally cytoreduced, more will be able to undergo intraperitoneal chemotherapy. Even patients with stage IV ovarian cancer experience improved survival with aggressive cytoreductive efforts.

Neoadjuvant chemotherapy may have a place for elderly patients who are not candidates for up-front aggressive surgery. Interval cytoreduction may be helpful if the original surgery was not performed by a gynecologic oncologist. Secondary cytoreduction can also improve survival, with the best candidate having a long recurrence-free interval and a smaller number of recurrence sites. These surgeries should be performed by gynecologic oncologists capable of performing aggressive/ultraradical cytoreductive procedures.

References
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44. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol 2006;103:559–564.


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1. In the United States, which of the following best describes how ovarian cancer ranks as a cause of cancer-related death?
   A. Second
   B. Third
   C. Fourth
   D. Fifth

2. The Gynecologic Oncology Group (GOG) defines optimal cytoreduction as which of the following?
   A. No residual disease
   B. 0.5 cm or less of residual disease
   C. 1 cm or less of residual disease
   D. 2 cm or less of residual disease

3. Which of the following is most likely to be considered standard treatment for ovarian cancer?
   A. Platinum agents with taxanes
   B. Doxorubicin with topotecan
   C. Gemcitabine
   D. Bevacizumab with methotrexate

4. Which of the following best describes median survival in patients with stage III or IV ovarian cancer who receive a greater than 75% compared with a 25% maximal cytoreductive effort, according to data from a meta-analysis of 53 studies?
   A. No change in survival
   B. Increased from 23 to 34 months
   C. Increased from 15 to 20 months
   D. Increased from 7 to 14 months

5. Which of the following is the most reliable preoperative test for predicting response to optimal cytoreduction in patients with ovarian cancer?
   A. Positron emission tomography (PET)
   B. CA-125
   C. Computed tomography (CT) of the abdominal organs
   D. None of the above

Activity Evaluation

1. The activity supported the learning objectives.
   Strongly Disagree 1 2 3 4 5
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