

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

Section Editor: Robert L. Coleman, MD

Management of Epithelial Ovarian Cancer



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H&O Is surgery always possible in patients with epithelial ovarian cancer?

ML Surgery is an integral part of the management of epithelial ovarian cancer. Sometimes surgery is not possible because the patient is too old or sick, or the disease burden is too high to allow an optimal resection. In those cases, we begin treatment with chemotherapy and then reassess the patient to see if surgery is an option. The vast majority of patients with epithelial ovarian cancer undergo surgery at some point.

H&O What are the goals of surgery for epithelial ovarian cancer?

ML The goals depend on the stage. Approximately 30% of patients present with early-stage disease—stage 1 or 2. In these patients, we remove the ovaries and possibly the uterus, and in order to stage the cancer we remove some lymph nodes and other abdominal tissue for biopsy. Surgery in patients with early-stage disease is often done using a minimally invasive approach.

Approximately 70% of patients present with advanced-stage disease—stage 3 or 4—in which cancer has spread to the abdomen or chest. In that case, we need to decide whether to conduct primary debulking followed by chemotherapy, or neoadjuvant chemotherapy followed by debulking. In the primary debulking approach, we perform surgery followed by 6 cycles of chemotherapy. In the neoadjuvant approach, we attempt to perform surgery after 3 cycles of chemotherapy, and administer the remaining 3 cycles of chemotherapy after surgery. Our

goal for surgery in advanced-stage ovarian cancer is to achieve an optimal cytoreduction.

H&O How is optimal cytoreduction defined?

ML Optimal cytoreduction was traditionally defined as removal of all the tumor in the abdomen, so that no more than 1 cm of tumor remains. More recently, the definition has become more stringent so that optimal cytoreduction requires that no gross residual tumor be present. This change is based on analysis and experi-

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ence that has been published over many years—we have learned that patients with no gross residual tumor have the best survival.

Two randomized clinical trials conducted outside the United States have looked at primary debulking vs debulking after neoadjuvant chemotherapy: one by Vergote and colleagues from Europe and Canada that was published in the *New England Journal of Medicine* in 2010, and the phase 3 CHORUS trial (Primary Chemotherapy Versus Primary

Table. Recommendation for Secondary Cytoreduction Based on Disease-Free Interval, the Number of Recurrence Sites, and Evidence of Carcinomatosis

DFI	Single Site	Multiple Sites: No Carcinomatosis	Carcinomatosis
6-12 mo	Offer SC	Consider SC	No SC
12-30 mo	Offer SC	Offer SC	Consider SC
>30 mo	Offer SC	Offer SC	Offer SC

DFI, disease-free interval; mo, months; SC, secondary cytoreduction.

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Surgery for Newly Diagnosed Advanced Ovarian Cancer) from the United Kingdom and New Zealand that appeared in the *Lancet* in 2015. In both of these trials, patients with ovarian cancer were randomly assigned to either primary debulking followed by 6 cycles of chemotherapy or neoadjuvant chemotherapy followed by surgery and then more chemotherapy. The studies found that median overall survival was just as good with the neoadjuvant approach, but the surgery was easier and led to fewer complications.

One disadvantage of these studies is that they both took place outside of the United States, where overall survival rates are much lower than those seen in the United States—especially in large academic centers such as ours. Median overall survival was 32 months in the Vergote study and 24 months in the CHORUS study. In contrast, the median overall survival in stage 3 advanced high-grade epithelial ovarian cancer at large centers in the United States, as seen in research by the Gynecologic Oncology Group (GOG), is at least 44 months and approaches 100 months in those who have a complete primary resection followed by chemotherapy. It is extremely difficult to extrapolate the results of these 2 studies to our own patient population.

At Memorial Sloan Kettering, we prefer primary debulking over neoadjuvant chemotherapy. The success of surgical cytoreduction is highly dependent on the surgeon's skill, and sometimes we need to go beyond removal of the uterus and ovaries and remove part of the colon and small bowel, the spleen, the diaphragm, part of the liver, or part of the gallbladder. These surgeries can be quite complex.

H&O When are multiple surgeons required?

ML The need for multiple surgeons is highly variable in both the United States and around the world, but at

our institution the primary surgeon typically handles all of the surgery. One exception is that we call in a specialist in liver surgery if the patient needs an extensive hepatic resection. At another institution, the gynecologic surgeon may call in a colorectal, hepatobiliary, or urologic surgeon to help.

H&O Which patients are candidates for secondary debulking?

ML We have looked extensively at secondary debulking at Memorial Sloan Kettering, and the head of ovarian cancer surgery, Dr Dennis Chi, has created a scheme that details who should be considered for this procedure (Table). Basically, we consider secondary surgery or secondary cytoreduction for any patient who has experienced a disease-free interval of at least 6 months and does not have carcinomatosis. After that, the decision depends on factors such as the patient's health status and the number of sites of recurrence. The German Society for Gynecology (AGO) has published their own criteria for secondary debulking, which include Eastern Cooperative Oncology Group (ECOG) performance status of 0, complete resection during first-line therapy, and ascites less than 500 mL.

H&O What are the most important trials to examine secondary debulking?

ML Numerous retrospective trials have looked at secondary debulking. More recently, 2 prospective randomized phase 3 trials on secondary debulking have been presented but not published. The first trial, called DESKTOP III (Study Comparing Tumor Debulking Surgery Versus Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer), was presented by Dr Andreas Du Bois at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO). This trial used the AGO criteria for secondary debulking, and randomly assigned patients who experienced a relapse to chemotherapy with or without surgery. The authors found an improvement in median progression-free survival with surgery among patients who had complete resection. These were preliminary results because the primary endpoint of overall survival was not yet available.

The second trial, called GOG-0213 (Carboplatin, Paclitaxel and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian, Epithelial, Primary Peritoneal, or Fallopian Tube Cancer), was presented by Dr Robert Coleman at the 2018 ASCO annual meeting. As in the first trial, the investigators randomly assigned patients with recurrent ovarian cancer to chemotherapy with or

without surgery, and found that progression-free survival was better with surgery. Again, overall survival was the primary endpoint. There was no overall survival advantage with surgery in GOG-0213, however.

H&O What recent advances have been made in the surgical management of ovarian cancer?

ML What might be considered an advance depends to some degree on your point of view. For example, surgeons at MD Anderson Cancer Center in Houston, Texas, have begun doing a laparoscopic assessment of all patients with advanced ovarian cancer to decide whether they can achieve a complete gross resection. In a study published in *Obstetrics and Gynecology* earlier this year, they concluded that laparoscopic triage assessment in advanced ovarian cancer resulted in high complete surgical resection rates. Does this approach really alter overall survival, or does it simply select for patients who will have a better, easier surgical procedure? What remains to be determined is whether this approach makes the overall cohort of patients live longer.

At our institution, we do not take the approach of using laparoscopy in all our patients. Instead, we follow a scoring system based on certain computed tomography scan characteristics, age and other patient factors, American Society of Anesthesiologists score, and preoperative CA-125 level. Patients with a low score have a very high chance of optimal or complete gross resection, so we go straight to laparoscopy. For patients with a high score, we go straight to laparoscopy, make an assessment, and do the big debulking surgery the same day instead of needing to bring the patient back for an additional procedure. Debulking surgery can easily take 5 or 6 hours, which means that we need to block out a large chunk of operating room time that we often cannot use, but that is a logistical issue—we do what makes the most sense for patient outcomes. We rely on our scoring algorithm to minimize the number of times we waste operating room time.

H&O When is fertility preservation possible in epithelial ovarian cancer?

ML We discuss fertility preservation with patients who have stage 1 epithelial ovarian cancer and wish to maintain their fertility. We prefer that patients be younger than 45 years, but that is not an absolute cutoff. If the patient is truly stage 1 and the cancer affects only one ovary and there is no spread to the uterus or lymph nodes, the patient retains her uterus and her healthy ovary and is able to attempt pregnancy after chemotherapy is completed. Some oncologists will attempt fertility preservation in

patients with stage 2 epithelial ovarian cancer, but this is outside the realm of comfort for most of us.

H&O When is minimally invasive surgery recommended?

ML Minimally invasive surgery is the most common approach used in women with early-stage disease, for both staging and resection. For women with advanced ovarian cancer, minimally invasive surgery can be used for staging but has no role in primary tumor debulking, which requires a large laparotomy incision. Some patients with advanced ovarian cancer who have an excellent response to neoadjuvant chemotherapy—one that is confirmed through laparoscopy—may be candidates for minimally invasive procedures to remove the uterus, ovaries, and possibly the omentum. Laparoscopy can be an excellent tool in the setting of recurrent epithelial ovarian cancer, as shown in a retrospective study our group published in 2017 in *Gynecologic Oncology*, with Eriksson as the first author. There have not been any prospective studies published on this approach.

H&O Are there any other questions that need to be answered?

ML The question of primary debulking vs debulking after neoadjuvant chemotherapy has not been answered yet. We have our concerns regarding the studies that have been presented so far because the median overall survivals are far shorter than what we see here in the United States. One randomized international study that is looking at primary debulking vs neoadjuvant chemotherapy is TRUST (Trial on Radical Upfront Surgical Therapy; ENGOT-ov33/AGO-OVAR OP.7) from the AGO. This study has stringent requirements regarding qualifications for surgeons and institutions, and has already begun recruiting patients. My colleagues at Memorial Sloan Kettering will be opening a US-specific TRUST study in the next few months.

Another question regards the role of hyperthermic intraperitoneal chemotherapy (HIPEC). Some institutions are promoting their use of HIPEC, but that is premature given the lack of level 1 evidence at the time of primary cytoreduction. HIPEC is not without risk; it adds more than 90 minutes to surgery and may carry its own toxicities.

In a phase 3 trial published in the *New England Journal of Medicine* earlier this year, patients who had received 3 cycles of neoadjuvant chemotherapy were randomly assigned to receive interval cytoreductive surgery either with or without HIPEC. Overall survival and recurrence-free survival were significantly longer

with the addition of HIPEC, without an increase in the rate of adverse effects. This is the only randomized trial of HIPEC in the up-front setting for ovarian cancer. Here at Memorial Sloan Kettering, we are conducting a randomized phase 2 study that is looking at HIPEC in patients who are undergoing secondary cytoreduction; patients are randomly assigned to receive surgery plus HIPEC or surgery alone

Disclosure

Dr Leitao has done ad hoc consulting and speaking for Intuitive Surgical.

Suggested Readings

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