

## Surgery for Epithelial Ovarian Cancer

Adnan Munkarah, MD

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The incidence of ovarian cancer varies around the world. Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States and Northwester Europe. The age standardized incidence rate is highest in Northern Europe at 13.3 case per 100,000. In the United States, the American Cancer Society estimates 21,650 new cases and 15,520 deaths related to ovarian cancer in 2008. It is the fifth leading cancer site following breast, lung, colo-rectal, and endometrium. It also represents the 5th leading cause of cancer death in women following lung, breast, colo-rectal, and pancreatic carcinoma. Approximately one in seventy women will develop the disease and one in 100 will die secondary to its progression. The median age of diagnosis is 63. No accurate data is available as to the incidence and impact of the disease in the Arab world. According to WHO data, the age standardized incidence rate varies between 2.6 cases per 100,000 in Northern Africa and 5.3 per 100,000 in Western Asia. The mortality rate ranges between 1.8 and 3.4 per 100,000.

### Surgical Staging for Clinical early-Stage Disease

The staging of epithelial ovarian cancer is based on histopathologic examination of tissues submitted at time of primary surgery. Women with early stage disease usually present with pelvic or adnexal masses. Initial evaluation would include a full history and physical exam, transvaginal ultrasound and/or CT scan or MRI and blood testing including serum Ca-125 level. This is usually followed by surgical exploration. The first step in the surgical procedure should include complete examination of the abdominal cavity followed by obtaining peritoneal washing. The pelvic mass with the affected ovary is then removed and sent to pathology for frozen section evaluation. Every attempt should be made to remove the mass intact without rupture and spillage of the contents into the peritoneal cavity in order to avoid upstaging. If a diagnosis of epithelial ovarian cancer is confirmed, a complete staging procedure will be performed including hysterectomy and contralateral oophorectomy, omentectomy, pelvic and periaortic lymph node dissection and multiple peritoneal biopsies including sampling of the diaphragm. Performing a complete staging is important for prognostic as well as therapeutic reasons. First, approximately 30% of women with disease apparently confined to the ovary will have histologic evidence of metastatic disease and will require chemotherapy following surgery<sup>2</sup>. Second, women with stage IA or IB and low-grade cancer do not need adjuvant chemotherapy. Other stage I patients might be candidate for an abbreviated adjuvant chemotherapy schedule<sup>3</sup>. In these women,

a complete and comprehensive staging might reduce the morbidity and cost of adjuvant therapy. Researchers from the European Organization for Research and Treatment of Cancer (EORTC) tested the efficacy of adjuvant chemotherapy for early-stage ovarian cancer in phase III randomized trial. They found that in optimally staged patients, chemotherapy did not improve survival. On the other hand, chemotherapy was associated with improved recurrence-free survival in the non-optimally staged group<sup>4</sup>.

Unfortunately, despite these recommendations, a large number of women with early stage ovarian cancer do not undergo complete staging<sup>5</sup>. Studies have shown that the specialty of surgeon performing the staging has a significant impact on how adequately the staging is performed. Complete staging is performed in 97% of patients cared for by a gynecologic oncologist, compared to 35-52% of patients evaluated by other surgeons.

In a subset of young women with early ovarian cancer, fertility preserving surgery is an acceptable therapy. Removal of the pelvic mass with the involved ipsilateral adnexa, while preserving the uterus and contralateral ovary, are recommended in a woman who desires future fertility and who has a low-grade lesion confined to one ovary. Complete surgical staging should still be performed to rule out peritoneal or lymphatic spread of the cancer.

### Surgical Management of Advanced Stage Disease

#### Primary Tumor Debulking Surgery

Women with advanced stage ovarian cancer frequently present with large volume ascites and extensive pelvic and intra-abdominal disease. In 1934, Meig was the first to describe primary debulking or cytoreduction in ovarian cancer. Pemberton in 1940 and Munnel described similar concepts in 1957. Griffiths was the first to publish data correlating the size of residual disease and survival in women with advanced ovarian cancer<sup>6</sup>. The beneficial effect of tumor debulking has been explained based on a number of theoretical hypotheses. First, it is believed that reducing the volume of the tumor will optimize the blood flow to the residual masses thus improving drug delivery, increasing the growth fraction of the tumor and improving response of the cells to chemotherapy. Second, since the number of chemoresistant cells is proportional to the total number of neoplastic cells, reducing the total number of cells will decrease the number of chemoresistant clones. Third,

the fractional cell kill hypothesis implies that the efficiency of chemotherapeutic agent is dependent on drug dosage and number of viable neoplastic cells. Removing a large percentage of the viable neoplastic cells surgically will leave a smaller number of cells for the chemotherapy to kill. Finally, it has been speculated that tumors can suppress the patient immune system and removing them may enhance immune function.

Since the initial publication by Griffiths in 1972, there have been a large number of retrospective studies that have confirmed a negative correlation between size of residual disease and survival. In a recently published meta-analysis of 81 cohort studies that included 6885 patients with stage III or IV ovarian cancer treated with surgery and platinum based therapy, Bristow et al showed a correlation between the proportion of maximal cytoreduction and median survival. They reported a 5.5% increase in median survival for each 10% increase in maximal cytoreduction. The median survival was 22.7 months in patient populations with <25% maximal cytoreduction compared to 33.9 months in those with >75% maximal cytoreduction<sup>7</sup>. Extended survival exceeding 4 years has been reported in stage IIIc ovarian cancer patients who were optimally debulked prior to receiving chemotherapy<sup>8,9</sup>.

There is an ongoing argument whether the beneficial effect of surgical cytoreduction are related to the surgical effort or is inherent to the tumor biology<sup>10</sup>. Some have proposed that the biologically less aggressive tumors are more amenable to optimal debulking but are also more likely to have a better prognosis independent of the surgical effort. A number of authors have tried to refute that argument by showing that the use of radical surgical procedures to achieve optimal debulking in more aggressive tumors is not associated with a worse prognosis<sup>11,12</sup>. They have also shown that the size of residual disease but not the extent of disease at initiation of surgery is an independent prognostic factor. Finally, a number of papers have also proved that the institution and surgeon's experience are important in achieving optimal surgical results and improving the survival of women with advanced ovarian cancer<sup>5,13,14</sup>.

The goal of surgical debulking is to remove all gross disease since this is associated with the best survival outcome. When left with macroscopic residual disease after tumor debulking, patients with largest residual tumor <1 cm tend to survive longer than those with >1 cm residual disease. Cytoreduction for advanced disease often requires removal of large pelvic tumors with en bloc resection of uterus, ovaries and rectosigmoid, omentectomy, bowel resection and removal of extensive peritoneal and diaphragmatic implants. The use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) and Argon Beam Coagulator can sometimes increase the success of cytoreduction. Significant surgical expertise and special training are required to perform radical ovarian cancer cytoreductive procedures. In addition, these women are usually older and have other medical illnesses. Optimal and aggressive perioperative care, with adequate intensive care support, is essential for a successful outcome.

### Secondary Tumor Debulking Surgery

In women whose primary surgery was suboptimal, the role of secondary surgery after primary surgery and 3 cycles of chemotherapy was investigated in 2 independent randomized trials one in Europe by the EORTC and the second in the United States by investigators from the Gynecologic Oncology Group (GOG)<sup>15,16</sup>. The findings of the 2 studies were conflicting. The EORTC study did find that women who underwent optimal secondary surgery had an improved survival. These findings were not confirmed by the GOG study. One possible explanation is the difference in maximal surgical effort at time of primary surgery. For women whose primary surgery involved a minimal attempt at tumor debulking,

a secondary debulking surgery may be valuable in improving patients' overall outcome. On the other hand, the role of secondary debulking may be limited in women whose primary surgery involved a maximal surgical effort even though optimal debulking could not be achieved.

### Interval Tumor Debulking Surgery

The use of neoadjuvant chemotherapy prior to any surgery has been reported in women with ovarian cancer cases who are too sick to undergo primary surgery. In addition, some authors have proposed using this approach in cases where extensive metastatic disease interferes with optimal primary cytoreduction. Proponents of this approach argue that the use of chemotherapy will increase the chances of achieving an optimal cytoreduction at time of interval surgery. In addition, the surgical complications of the interval debulking surgery are reduced because the tumor load is smaller and the patients are in a better physical condition<sup>17,18</sup>. However, not everyone is supportive of this approach. In a review of the published studies, Bristow and Chi concluded that neoadjuvant chemotherapy with interval debulking is associated with inferior survival compared to primary surgery<sup>19</sup>. However, they did find that in patients who underwent interval debulking, increasing percent maximal cytoreduction is positively associated with median survival.

### Surgical Management of Recurrent Disease

Despite the excellent response rates (around 70%) to primary therapy, over two thirds of women with advanced ovarian cancer suffer from disease recurrence. Treatment of recurrence is influenced by a number of factors including initial tumor histology, outcome of primary surgery, response to primary chemotherapy, time to recurrence, site of recurrence and coexisting medical illnesses. Women who recur over six months after initial response to platinum based chemotherapy, are considered to be platinum sensitive. In this subgroup, one option of salvage treatment includes reinduction with a platinum compound. Other drugs proven to be effective in the salvage therapy of recurrent ovarian cancer are topotecan, pegylated liposomal doxorubicin (doxil), gemcitabine, docetaxel, paclitaxel, navelbine, oral etoposide, hexamethylmelamine, ifosfamide, tamoxifen and bevacizumab. Women who fail within six months of platinum-based chemotherapy are considered platinum resistant. They can be offered one of the above listed drugs. Unfortunately, their disease tends to respond poorly to most drugs and their life span is usually limited.

A selected group of patients with recurrent disease may benefit from secondary cytoreduction. This includes women who have: a longer disease-free interval, a good response to initial treatment, a limited number of recurrent tumors that are surgically accessible, and a good physical condition. The patient should also be willing to be treated with chemotherapy (or less commonly radiation therapy) after recovery from surgery. The goal of secondary surgery for recurrent disease is resection of all gross disease. Prolonged survivals have been reported in some of these patients.<sup>20,21</sup> A number of factors have been associated with a higher likelihood of optimal secondary cytoreduction as well as prolonged survival. These include: younger age, longer recurrence free interval, complete clinical response to primary platinum chemotherapy and a good performance status. Two ongoing randomized clinical trials one by GOG and one by EORTC are evaluating the role of surgery for recurrent disease.

In conclusion, surgery plays an important role in the management of epithelial ovarian cancer. At diagnosis, optimal staging or debulking surgeries are important to secure patients the best survival outcome. At recurrence, surgery needs to be considered as an option in some patients. Many studies have shown that the

expertise of the specialist surgeon has a significant impact on survival. The initial staging and resection in primary disease as well as the appropriate decision and surgical procedure in recurrent disease are best handled by specialized surgeons who have been trained in the field and who routinely manage ovarian cancer in their practice.

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