SURGICAL TECHNIQUES

Christina S. Chu, MD
Assistant Professor, Division of Gynecologic Oncology,
Department of Ob/Gyn, University of Pennsylvania Medical Center, Philadelphia
Stephen C. Rubin, MD
Professor and Chief, Division of Gynecologic Oncology,
Department of Ob/Gyn, University of Pennsylvania Medical Center, Philadelphia

Ovarian cancer: What can we expect of second-look laparotomy?

It is the only way to confirm a complete pathologic response to therapy and individualize the prognosis.

The disturbing fact that epithelial ovarian cancer often recurs after clinical remission poses this challenge: How do we identify the women with subclinical disease who may benefit from additional consolidation therapy?

Given the inability of noninvasive studies such as computed tomography, magnetic resonance imaging, and positron emission tomography to reliably detect small-volume and microscopic disease, second-look laparotomy (SLL) is the only technique capable of confirming a complete pathologic response to therapy.

Ob/Gyns involved in care of women with advanced ovarian cancer face the challenge of weighing the benefits of SLL against the potential morbidities of invasive surgery. This article describes those benefits, surgical technique, the prognostic significance of findings, and the status of salvage and consolidation therapies.

KEY POINTS

- **Second-look laparotomy (SLL)** is the only way to confirm complete pathologic response to ovarian cancer therapy.
- **Offer SLL only to patients** for whom results will affect decision-making—and only after discussion with the patient and a gynecologic oncologist.
- **Although negative SLL findings** confer improved prognosis, disease recurs in up to 60% of patients.
- **Candidates should be in clinical remission** as determined by physical examination, abdominopelvic imaging, and serum CA-125 determination.

What SLL conveys

"Second look laparotomy" has rather loosely described many secondary surgeries for ovarian cancer, but we adopt the more rigorous definition: "a systematic surgical reexploration in asymptomatic patients who have no clinical evidence of tumor following initial surgery and completion of a planned program of chemotherapy."[1]

Procedures to debulk recurrent or residual disease, relieve symptomatic tumor, or accomplish interval cytoreduction cannot be deemed second-look laparotomy.

Prognostic, therapeutic limitations complicate the decision

Although negative findings at SLL confer an improved prognosis, disease ultimately recurs in up to 60% of patients.[2,3]

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TABLE

Components of second-look laparotomy

Vertical incision
Thorough inspection of abdomen and pelvis
Abdominopelvic washings for cytologic analysis
Complete adhesiolysis
Systematic biopsy of: Undersurfaces of bilateral hemidiaphragms Paracolic gutters Pelvic peritoneum Pedicles of ovarian vessels Any suspicious lesions Areas of known prior tumor Adhesions
If necessary: Complete hysterectomy, salpingo-oophorectomy, omentectomy, and appendectomy
Pelvic and paraaortic lymph node sampling

SLL detects residual disease in 30% to 50% of patients.

Moreover, despite intensive research, consistently effective consolidation and salvage regimens remain elusive.

SLL may provide some information about prognosis, but that information is far from certain. Because of the cost and morbidity inherent in SLL, routine use has largely been limited to patients in clinical trials, where findings may serve as a surrogate endpoint for investigational therapies.

For these reasons, we strongly recommend careful discussion of this complex decision with patients prior to surgery, in consultation with a gynecologic oncologist.

Which patients are and are not candidates?

Candidates should be in clinical remission as determined by physical examination, abdominopelvic imaging, and serum CA-125 determination. Although SLL will detect residual disease in up to 50% of patients undergoing the procedure after primary chemotherapy, SLL is an imperfect method of determining the true response to therapy. Thus, it should be offered only to patients for whom results will influence clinical decision-making.

Patients with stage I disease treated with appropriate chemotherapy should not undergo SLL because of the low incidence of positive findings.[4]

Residual disease: 30% to 50%

Second-look laparotomy requires thorough inspection of the peritoneal cavity and retroperitoneum, but when properly performed on appropriate candidates, SLL detects residual disease in 30% to 50% of patients.[2,5]

Generally, stage and volume of residual disease at initial surgery are most closely correlated with findings. In a review of 31 series, patients with stage III and IV disease undergoing surgery had fewer negative SLLs (39% and 33%, respectively) than patients with stage I and II disease (81% and 69%, respectively).[6] Similarly, in pooled data on 1,797 patients, 72% of those with no gross residual disease at the conclusion of primary surgery had negative findings at SLL, compared with 50% of those with optimal residual, and only 23% of those with suboptimal residual.[6]

Surgical technique

Surgery begins with a large vertical incision and involves the components listed in the **TABLE**.

If gross disease is apparent:

Consider surgical cytoreduction, which is typically performed at the surgeon's discretion.

In the absence of gross tumor:

Use a 5-point strategy to search thoroughly for occult disease.

- Take washings for cytology from the abdomen and pelvis;
- lyse any adhesions to allow adequate examination of all peritoneal surfaces;
- obtain random biopsies from the pelvis, bladder serosa, vaginal cuff, cul-de-sac, paracolic gutters, and hemidiaphragms, as well as adhesions, sites of prior documented tumor, infundibulopelvic ligament pedicles, and areas

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suspicious for tumor recurrence;
- consider removing the uterus, adnexae, omentum, and appendix, if not done at the primary surgery; and
- sample any remaining pelvic and paraaortic lymph nodes.

Meticulous sampling is crucial

Although the number of biopsies performed at SLL varies widely by surgeon, meticulous sampling of peritoneal surfaces may be necessary to detect occult tumor. In cases of microscopic disease, fewer than 5% of biopsies may be positive for tumor.[7] Not surprisingly, some studies have noted a significantly worse survival rate among patients deemed to be in complete pathologic remission who underwent fewer biopsies at the time of SLL.[8]

What do SLL findings predict?

Survival rates

Women who achieve a complete pathologic response after primary chemotherapy have the greatest survival. Rubin et al[3] noted a 10-year survival rate of 51% for 91 patients after negative SLL. Median survivals for patients with negative findings have been reported in excess of 70 months.[7,9] Tuxen et al[9] examined 242 patients after SLL and reported a median survival of 149 months for those with negative findings, versus 39 and 24 months for those with microscopic and gross disease, respectively ($P<.0005$).

Survival rates among women with negative findings were substantially higher than among patients with positive findings, even though the latter group received salvage chemotherapy.

Recurrence rates

In a review of 38 studies encompassing 1,511 patients, Barter and Barnes[6] noted a 23% rate of recurrence among women with negative findings at SLL. Other studies from single institutions document recurrence rates approximating 50%.[3,10] Patients experiencing recurrence after negative SLL have median survivals of 11 to 45 months.[3,8,10-12]

Gross versus microscopic disease

Studies comparing outcomes based on volume of disease detected at SLL have found statistically improved survival for patients without evidence of gross tumor.[9,13-15] Podratz et al[14] reported 4-year survival of 55% for women with microscopic findings versus 19% for those with gross disease ($P<.01$).

The presence of gross tumor at SLL indicates a grave prognosis; median survival ranges between 13 and 24 months.[9,16,17] Nevertheless, several studies have shown that patients able to undergo debulking of all visible disease derive a survival benefit.[4,15,18,19]

Given the potential complications of extensive debulking surgery and lack of a proven survival benefit for patients unable to achieve complete cytoreduction, debulking should only be attempted if persistent disease is judged to be completely resectable.

When SLL is positive: Salvage therapy regimens

Many different salvage regimens for epithelial ovarian cancer have been investigated for use after positive second-look laparotomy, including intraperitoneal radioactive phosphorus (^{32}P), systemic chemotherapy, whole abdominal radiation (WAR), hormonal therapy, and biologic response modifiers. Unfortunately, studies of salvage therapy tend to be retrospective, nonrandomized, and uncontrolled, and no proven regimen has yet been found.

Whole abdominal radiation

This modality appears to confer no definitive survival benefit and does produce toxicity. MacGibbon et al[20] treated 51 patients with WAR for both salvage and consolidation. Of these, 27% could not complete

Median survival after negative findings can exceed 140 months.

treatment because of progressive disease, bowel perforation, myelosuppression, and bowel toxicity. An additional 24% required treatment delays because of hematologic and gastrointestinal toxicity. Among those completing the prescribed course of radiation, 6 developed late bowel symptoms, and 2 of these required surgical intervention to relieve bowel obstruction.

Other salvage therapies

Recently, Dowdy et al[18] reported long-term follow-up for 145 patients with positive findings at SLL. Neither intraperitoneal ^{32}P nor WAR provided a survival benefit. Multivariate analysis indicated that only grade and volume of residual disease following cytoreduction were associated with improved survival.

Other trials involving intraperitoneal interferon-alpha and carboplatin,[21] and high-dose chemotherapy with autologous stem cell rescue[22] have also failed to demonstrate any significant advantages in survival or rate of progression. An early phase II study of intraperitoneal paclitaxel showed promise: Markman et al[23] noted a complete pathologic response in 61% of patients with microscopic disease at SLL, but only 4% of those with gross disease achieved a complete response.

Attempt debulking only if persistent disease is deemed totally resectable.

Need for effective consolidation therapy

A critical component of cancer care is targeting patients at highest risk of recurrence for effective consolidation therapy. The factors most strongly correlated with disease progression are stage at diagnosis, tumor grade, and volume of residual disease after initial cytoreduction.

Many consolidation therapies have been described, including systemic and intraperitoneal chemotherapy, WAR, intraperitoneal ^{32}P, and biologic response modifiers.

Significant risk of distant recurrences

Although most tumors recur in the abdomen and pelvis, approximately 30% recur at distant locations. For this reason, consider systemic treatment when planning the consolidation regimen. Bertucci et al[22] studied systemic melphalan-based, high-dose chemotherapy with autologous stem cell rescue and noted a 5-year progression-free survival of 43% and overall survival of 75%.

Most therapies are localized. Most other studies have focused on therapies localized to the peritoneal cavity. Results for intraperitoneal ^{32}P and WAR are mixed. Several different regimens of intraperitoneal chemotherapy have produced median disease-free survival rates of 18 to 41 months.[24-27] In 1998, Barakat et al[27] examined the use of intraperitoneal cisplatin and etoposide, reporting a statistically improved median disease-free survival for patients receiving intraperitoneal consolidation (median disease-free survival not yet reached), compared with patients treated by observation (28.5 months).

Bottom line

Second-look laparotomy reveals that approximately 50% of patients with a complete clinical response still harbor residual disease after primary chemotherapy. Even women who achieve a complete

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for treatment details and outcome data from the research on:

- **salvage regimens** after positive second-look laparotomy, and
- **consolidation therapies** after negative second-look laparotomy.

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Is laparoscopy equal to laparotomy for second-look procedures?

Advocates of laparoscopy as a substitute for SLL report lower blood loss, shorter hospitalization, and decreased costs for laparoscopy.[28]

Clough et al[29] performed the first study of second-look laparoscopy in 20 patients, using immediate laparotomy as a control. In 12 patients, adequate exploration was hindered by adhesions, and only 2 were able to undergo sufficient laparoscopic adhesiolysis. Overall, only 41% of patients could be completely explored at laparoscopy, versus 95% for laparotomy. However, obvious carcinomatosis was apparent in 3 patients at laparoscopy, rendering laparotomy unnecessary.

In general, laparoscopic second look has been reported to be a safe, feasible alternative to laparotomy. Although intraabdominal adhesions occur in as many as 70% of patients,[30,31] complete laparoscopic evaluation may still be possible in up to 92%.[32,33]

How accurate?

Concerns remain about the accuracy of laparoscopic second look. Prior to 1985, several studies reported false-negative rates of 19% to 77%,[33,34] although a 1999 study documented a false-negative rate of only 14%.[29] The clinical impact of these false negatives is controversial. Some authors have reported no differences in clinical endpoints such as disease recurrence[28] and overall survival[35] for patients undergoing laparoscopy versus laparotomy. In contrast, a multivariate analysis by Gadducci et al[10] showed a significantly prolonged disease-free interval for patients treated by laparotomy.

Switch to laparotomy for maximal cytoreduction

Laparoscopy may spare patients with obvious unresectable carcinomatosis a full laparotomy, though many patients will still require conversion to an open procedure to achieve maximal cytoreduction. Given these considerations, laparoscopy has only a limited role in second-look evaluation.

Laparoscopic second look has a false-negative rate of at least 14%.

pathologic response have recurrence rates as high as 60%. While SLL can be a useful tool, the information it yields must be weighed against the potential morbidities of invasive surgery. Given its limited prognostic value, SLL should be offered only when results will influence clinical decision-making, or as part of a clinical trial. ■

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By Anne M. Weber, MD, MS

Associate Investigator,
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