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Epithelial Ovarian Cancer: Evaluation, Staging, Surgery, and Stage I and II Disease Management

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Epithelial Ovarian Cancer: Evaluation, Staging, Surgery, and Stage I and II Disease Management

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INTRODUCTION

Ovarian cancer is the second most common gynecologic cancer among women in the United States. It is also the fifth leading cause of cancer mortality in women and the leading cause of death among women with gynecologic malignancies. The American Cancer Society statistics released in 2015 estimate that 21,290 new cases of ovarian cancer will occur during the year, with approximately 14,180 deaths.¹ Globally, there were 238,719 new cases of ovarian cancer diagnosed in 2012, representing 3.6% of all cancers in women, and nearly 151,905 deaths.² The highest incidence of ovarian cancer occurs in northern, central, and eastern Europe, followed by western Europe and North America, with the lowest incidence in parts of Africa and Asia. The majority of women presenting with ovarian cancer will present at an advanced stage, and the 5-year survival in this group is less than 30%.³

In this review, the first of 2 articles on ovarian cancer, the clinical case will guide the discussion of presenting symptoms and workup of ovarian

cancer and the management of stage I and stage II disease, based on the literature and present standard of care. The second article will be published in the *Oncology Board Review Manual*, Volume 11, Part 3, and focus on the management of advanced stage ovarian cancer.

EPIDEMIOLOGY AND RISK FACTORS

Epithelial ovarian cancer was originally thought to derive from malignant transformation of the ovarian surface. However, in studying patients with the high-grade serous subtype, recent reports have now postulated that the origin may be the fallopian tube,^{4,5} and molecular evidence has been reported in a developed mouse model.⁶

The average lifetime risk of developing ovarian cancer in the U.S. general population is 1.4% to 1.8%, and multiple risk factors can predispose a woman to developing the disease.^{7,8} These risks include age, with a median age at diagnosis of 60 years, early menarche, and late menopause, as well as nulliparity,⁹⁻¹² which has been hypothesized to be related to increased trauma and repair to

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the ovarian epithelium due to uninterrupted cycles of ovulation. Also, using estrogen alone for more than 10 years in the postmenopausal setting as hormone replacement therapy increases the risk of ovarian cancer; this risk was reported to persist for up to 29 years after estrogen was stopped.¹³ Talc in talcum powder used on the perineum or on sanitary napkins may be associated with increased risk of ovarian cancer.¹⁴

In contrast, the use of oral contraceptives,^{15,16} an increased number of pregnancies,¹⁷ and breastfeeding¹⁸ have been shown to reduce ovarian cancer risk. Tubal ligation has also been correlated with a reduced risk of ovarian cancer, although the mechanism is unknown.¹⁹ Also, although additional studies are recommended, the recent reports on treatment of infertility and risk for ovarian cancer do not substantiate a correlation.^{20,21} The risks for developing ovarian cancer were evaluated in a case-control study in Sweden, which supported the findings noted in previous studies, showing no correlation between treatment for infertility and the development of ovarian cancer.²²

Ovarian carcinomas are now divided into 5 main groups based on histopathology and genetics: high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous types. In addition, histologic subtype can also determine prognosis.²³

Family history is an important risk factor for developing ovarian cancer. Women with 1 affected relative have a 5% estimated lifetime risk of developing ovarian cancer, while women with 2 affected relatives have an estimated risk of 7% (in contrast to an estimated risk in the general population of 1.6%).²⁴ In the hereditary ovarian cancer syndromes, the lifetime risk of developing ovarian cancer ranges from 25% to 50%. Overall, hereditary ovarian cancer syndromes may account for up to 10% to 15% of all ovarian cancer cases.²⁵

Genetic testing of patients with ovarian carcinoma should be in accordance with the recently updated National Comprehensive Cancer Network (NCCN) guidelines (version 1.2015).²⁶

Hereditary ovarian cancer syndrome presently includes the 2 *BRCA* genes, *BRCA1* and *BRCA2*. Women carrying a *BRCA1* germ-line mutation have been estimated to have a lifetime risk of ovarian cancer ranging from 16% to 62%,^{27,28} while the lifetime risk of ovarian cancer for women with a *BRCA2* germ-line mutation has been estimated to be 10% to 15%.^{29,30}

Studies have suggested that ovarian cancers occurring in *BRCA* mutation carriers have a better prognosis compared to cancers occurring in the general population.^{22,31–33} Histopathology is typically high-grade serous for the *BRCA* group; there is an association reported between *BRCA2* and clear cell histopathology, but research is still ongoing.³⁴

Another familial syndrome associated with ovarian cancer is the Lynch syndrome, which is associated with mutations in the DNA mismatch repair genes *MSH2* and *MLH1*. Carriers of these germ-line mutations are most likely to develop colorectal cancer or endometrial cancer, but also have an elevated risk for ovarian cancer, with an estimated lifetime risk of 9%.³⁵ Also, there are less common mutations in genes, such as *RAD51D*, which can predispose women to a 1 in 11 chance of developing ovarian cancer.³⁶

CLINICAL EVALUATION AND INITIAL MANAGEMENT

CASE PATIENT

Initial Presentation and Evaluation

A 45-year-old G0 woman who has experienced a several-month history of irregular periods followed by the presence of discomfort in the left

lower quadrant presents several months after the start of her symptoms to her primary care physician, who considers the diagnosis of diverticulitis. She undergoes a computed tomography (CT) evaluation, which shows no active diverticular disease, but the left adnexal area is difficult to define. She follows up with her gynecologist, who orders a transvaginal ultrasound (TVUS). This reveals a septated and cystic left ovary measuring 10.5 × 6.0 cm. The right ovary is normal in appearance and size.

- **What are the signs and symptoms of epithelial ovarian cancer?**

CLINICAL FEATURES

The symptoms of ovarian cancer may be subtle or intermittent and mimic gastrointestinal issues such as gastroesophageal reflux disease (GERD) or a change in routine bowel habits. Given this presentation, patients may be initially referred to the gastroenterologist for evaluation, including endoscopy workup. Symptoms can also include vague abdominal discomfort, bloating, early satiety, constipation, indigestion, fatigue, urinary pressure/incontinence, and rarely, vaginal bleeding.^{37–39} A retrospective survey suggests that these symptoms may occur in the majority of patients prior to their diagnosis,⁴⁰ but early diagnosis remains difficult due to their nonspecific nature. It is possible but unusual for patients to present with acute symptoms due to ovarian tumor rupture or torsion.

Less commonly, ovarian cancer can also be associated with several paraneoplastic syndromes. The sign of Leser-Trélat, a rare phenomenon characterized by a sudden eruption of pruritic seborrheic keratoses, has been reported with ovarian cancer.⁴¹ Symptoms of paraneoplastic syndromes may precede the diagnosis. These entities can

include humoral-mediated hypercalcemia of malignancy (associated with clear cell carcinomas of the ovary),⁴² as well as subacute cerebellar degeneration.⁴³ Trousseau syndrome, a superficial migratory thrombophlebitis, has also been associated with ovarian cancer resulting in thrombosis.⁴⁴ A general review of rheumatologic disorders and associated paraneoplastic features involving ovary is discussed by Racanelli and colleagues.⁴⁵

- **What diagnostic studies should be performed for patients with suspected ovarian cancer?**

DIAGNOSTIC WORKUP

The workup for a woman suspected of having ovarian cancer should include a full physical examination to assess for adnexal mass, pleural effusion, and ascites. TVUS provides an initial evaluation of the pelvis. Features which can be found on the ultrasound and are associated with a malignant ovary include the presence of a complex ovarian cyst with either solid and/or cystic components, septations, ascites, peritoneal masses, or enlarged lymph nodes.⁴⁶ However, in primary peritoneal carcinoma, which is treated the same as ovarian carcinoma, a mass will not be present, but other features such as abdominal pain, effusions, ascites, and adenopathy will be noted.⁴⁷

A full staging CT exam is appropriate to confirm the extent of disease present. Also, labs including complete blood count (CBC) with differential, comprehensive chemistry, and tumor markers such as CA-125, carcinoembryonic antigen (CEA), and CA19-9 (if gastrointestinal primary is considered) can be ordered. CT findings can demonstrate a thickened omentum (cake), ascites, pelvic or adnexal mass, or hydronephrosis. The CA-125 level can either be elevated or within the normal range,

but using the combination of CA-125 and CEA can differentiate between ovarian and non-ovarian malignancy.⁴⁸

When working up typical findings of ascites or pelvic mass, other possible malignancies should be considered, including those which can metastasize to the ovary, as well as other primary malignancies. Signet-ring cell neoplasms, which originate from primary gastric carcinomas and metastasize to the ovaries bilaterally, can form Krukenberg tumors. Other primary sites that can metastasize to the ovary include upper and lower gastrointestinal tract cancers,⁴⁹ breast cancer⁵⁰ as well as primary lymphomas, which can present with adenopathy.⁵¹

CASE CONTINUED

Staging CT including the chest does not show evidence of distant metastatic disease. Her family history is without malignancy per her report. The CA-125 is elevated at 370 U/mL.

- **What is the significance of the CA-125 level?**

CA-125 levels are elevated in approximately 80% of postmenopausal women with advanced disease, but an elevated level is not always diagnostic of disease.^{52–54} CA-125 levels can be elevated with any disease or inflammation affecting the pleural or peritoneal lining. This can include other malignancies such as breast and lung cancer as well as benign conditions such as endometriosis, uterine leiomyoma, and pelvic inflammatory disease, inflammatory diseases, and physiological conditions.⁵⁵ CA-125 levels are known to fluctuate with the menstrual cycle. The marker can also be elevated in women with cirrhosis.⁵⁶ The use of CA-125 as a screening test is limited by its poor sensitivity in early-stage disease, with CA-125 levels elevated in only 50% of patients with

stage I disease. Additionally, approximately 1% of healthy women have a minimally elevated CA-125 level.⁵⁷

A human epididymis protein 4 (HE4) assay was approved by the U.S. Food and Drug Administration (FDA) in 2011 for use with the CA-125 as a quantitative test developed to aid the gynecologic surgeon. The Risk of Ovarian Malignancy Algorithm (ROMA), which derives a numerical score from the results of the CA-125 and HE4 blood tests, as well as menopausal status, defines which patients with newly found adnexal masses will be considered high risk and found to have malignancy. Results of this study showed a sensitivity of 88.4% and a specificity of 67.2% in both pre- and postmenopausal women.⁵⁸

- **Are there effective screening methods in detecting ovarian cancer?**

SCREENING

Screening for ovarian cancer is not currently recommended for the general population but may be appropriate for those considered at high risk (those with a strong family history of ovarian, breast, colon, or prostate malignancy or with known *BRCA* mutations). When evaluating women who have been diagnosed with ovarian cancer, they should be screened for *BRCA* mutation as per the NCCN guidelines (version 2.2014).⁵⁹

Several clinical trials have attempted to validate a screening program. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large population-based randomized study sponsored by the National Cancer Institute (NCI). It has collected data on the effects of cancer screening in men and women aged 55 to 74 years. However, in the ovarian group, the use of TVUS and CA-125 did not reduce ovarian cancer mortality.⁶⁰

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a prospective, randomized trial which has accrued more than 200,000 postmenopausal women aged 50 to 74 years.⁶¹ The study began recruiting women in 2001 in the UK. These women were then randomized to 3 arms: control arm with no screening, annual screening with TVUS, or annual CA-125 screening interpreted using a risk of ovarian cancer algorithm which adds serial measurements of CA-125 with TVUS as a second-line test. The endpoint of the study is to show an effect on mortality. The accrual was completed in 2005 showing that a screening program could be possible using these tests, and the women are being followed until 2015.⁶¹ The most recent publication evaluated the psychological morbidity associated with ovarian cancer screening.⁶²

Other screening modalities include the Risk of Ovarian Cancer Algorithm (ROCA). This strategy utilizes a mathematical model based on the patient's age and CA-125 score calculated over time, and patients are stratified into 1 of 3 risk groups, with the high-risk group referred for TVUS and to a gynecologic surgeon. Of the 10 women who had surgery based on TVUS, 4 invasive cancers were found, stages IA to IIB. The specificity was 99.9%. The authors concluded that ROCA followed by TVUS had excellent specificity for the average-risk population of women.⁶³

- **What is the next appropriate step in the evaluation and initial management of a patient with suspected ovarian cancer?**

SURGICAL MANAGEMENT

General Surgical Concepts

Cytoreductive surgery has played an important role in the management of advanced ovarian cancer since Griffiths demonstrated in 1975 that an in-

verse relationship existed between overall survival and residual tumor size.⁶⁴ This has been confirmed in subsequent studies, and a meta-analysis of 81 cohorts of patients with stage III or IV disease from clinical trials conducted between 1989 and 1998 suggested that for every 10% increase in the proportion of patients achieving maximal cytoreduction (defined in this meta-analysis as residual disease ≤ 3 cm in maximal dimension), there was an approximate 5.5% improvement in length of overall survival.⁶⁵

The exact degree of debulking required to classify a cytoreductive procedure as "optimal" has undergone revision. Currently, the accepted Surgical Gynecologic Oncology Group definition states that optimal cytoreduction has been achieved if there is no gross residual.⁶⁶ Primary cytoreductive surgery is the present standard procedure in management of ovarian disease, with studies noting that maximal cytoreduction remains the basis for successful management of ovarian cancer.⁶⁷

For women with suspected ovarian cancer based upon radiologic imaging, physical examination, and laboratory data, surgical consultation with a gynecologic oncologist is the next step in the evaluation since it has been reported that patients are more likely to receive an optimal cytoreductive procedure when the operation is performed by a gynecologic oncologist.^{68,69} If indicated, the gynecologic oncologist will perform a cytoreductive procedure including total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, and careful examination of all bowel and organ surfaces. Biopsy samples are taken from the peritoneal surfaces, including the diaphragm, and sampling of the para-aortic and pelvic lymph nodes can be performed. Any peritoneal fluid is sent for cytologic evaluation.

Surgery in Advanced Disease

The concept of optimal cytoreduction in advanced disease has been reviewed by Markman,⁷⁰ with the conclusion that the benefits of primary surgical cytoreduction in advanced stage patients need to be supported by clinical trial data. There was good evidence that the size of the postoperative residual tumor was prognostic and is the topic of several phase 3 studies.

Several prospective studies put forth by the AGO-OVAR and GINECO looked at the role of surgical outcome as the prognostic factor in advanced disease. There were 3126 patients evaluated within each of 3 groups: complete resection, small residual (1 to 10 mm), or residual exceeding 1 cm.⁷¹ The multivariate analysis demonstrated improved progression-free survival (PFS) and overall survival (OS) for those women who achieved complete resection compared with the other 2 groups ($P < 0.0001$). Additional independent prognostic factors included age, performance status, grade, stage, and histology. The conclusion was that the goal of primary surgery should be complete resection.⁷¹ However, patients with findings which could exclude successful surgery such as large-volume disease which is unresectable, or lung, mediastinal, or pleural involvement may benefit from a neoadjuvant approach.

The results from the EORTC-NCIC randomized study EORTC55971 suggested neoadjuvant chemotherapy (NACT) could be an alternative to the standard treatment approach in this subgroup of women with advanced disease.⁷² The results from this study demonstrated that NACT followed by interval cytoreductive surgery was not inferior to primary surgery followed by chemotherapy for patients with stage IIIc or IV disease. In this study, 670 patients with biopsy-proven invasive epithelial ovarian carcinoma, primary peritoneal carcinoma,

or fallopian-tube carcinoma were randomized to either receive primary cytoreductive surgery followed by adjuvant chemotherapy or NACT followed by interval cytoreductive surgery and then additional platinum-based chemotherapy. Complete resection of all macroscopic disease (1 cm or less) was the strongest independent variable for predicting OS in both groups. The median OS in the group receiving primary surgery was 29 months and in the initial NACT group, 30 months. The hazard ratio (HR) for death in the NACT/surgery group compared with the surgery/chemotherapy group was 0.98 ($P = 0.01$ for noninferiority). The author concluded that NACT/surgery resulted in the same survival but with fewer complications than performing primary cytoreductive surgery on this group.⁷²

The MRC CHORUS trial (CRUK 07/009) is the other randomized phase 3 trial evaluating when to perform surgery in advanced ovarian cancer patients.⁷³ The group included stage III-IV patients who were randomized to either standard treatment (primary surgery followed by 6 cycles of chemotherapy) or NACT (3 cycles of chemotherapy followed by cytoreductive surgery then completion chemotherapy). This trial was also designed as a noninferiority study. Primary outcome was OS and secondary outcome was PFS. A total of 550 women were randomized into the 2 well-balanced groups. The median OS was 22.8 months for the primary surgery group and 24.5 months for the NACT group, with the HR of 0.87 favoring the NACT group. The PFS was 10.2 months in the primary surgery group and 11.7 months in the NACT group. The conclusion was that NACT allowed for increased optimal cytoreduction, less early mortality, and similar survival. These results are consistent with the results found in the EORTC55971 trial regarding the role of NACT as an alternative in this group of woman with advanced disease.⁷³

Experience from Memorial Sloane Kettering Cancer Center using the same patient criteria showed that only 10% of these patients received NACT, with optimal cytoreduction (<1 cm) achieved in 71% of the patients. The PFS was 17 months, while the OS was 50 months. The conclusion was that primary cytoreductive surgery should remain the standard of care for the majority of women with advanced ovarian carcinoma, as reported at the 9th International Conference on Ovarian Cancer.⁷⁴

STAGING

Stage is an important factor in determining prognosis and treatment for ovarian carcinoma. Based upon the findings from surgery, staging is determined according to the American Joint Committee on Cancer and International Federation of Gynecologic Oncologists (FIGO) joint staging system (**Table 1**). FIGO staging is used exclusively in gynecologic malignancies, but one can correlate with the TMN staging used for all other solid tumor types.

CASE CONTINUED

The patient is referred to a gynecologic surgeon for consultation and, given the abnormality of the left ovary, a standard cytoreductive surgery with TAHBSO, omentectomy, diaphragm and gutter biopsies as well as washings are recommended. At surgery, endometriosis is noted scattered throughout the surgical field with adhesions, and the left ovary is stuck to the pelvic sidewall. The omentum is without disease upon visual inspection and the nodes are palpably normal. A small amount of pelvic fluid is obtained for diagnostic analysis. At the time of dissection of the left ovary, there is evidence of rupture, but the ovary is able to be removed in total. The right ovary is of normal size, the surrounding adhesions are able to

be dissected away, and it is removed intact. The final pathology report indicates the left ovary to be malignant, grade 2, endometrioid type with rupture and surface involvement, and the fluid is negative for malignancy as were the fallopian tubes, uterus, bilateral pelvic nodes sampled, and omentum. Her stage is IC2.

MANAGEMENT OF STAGE I AND STAGE II DISEASE

Treatment decisions are based on stage of disease, and the NCCN guidelines serve to outline management decisions. The NCCN was initially formed in 1995 with 13 academic cancer institutions. The goals included providing clinical practice guidelines to establish uniform quality cancer care. There are now 23 member institutions across the United States whose board members actively update the guidelines based on scientific developments.²⁶

- **What are the treatment options for early-stage ovarian cancer?**

EARLY-STAGE DISEASE

Early-stage (stage I disease) is associated with a significantly better prognosis, with 5-year survival ranging from approximately 65% to over 90%.⁷⁵ In contrast, 5-year survival for stage III and stage IV disease is estimated to be less than 40% and less than 20%, respectively. However, even for patients diagnosed with early-stage disease, there is a significant risk of recurrence depending on the histologic subtype, and these patients should receive adjuvant chemotherapy following surgical resection as noted in the NCCN guidelines.²⁶

The NCCN guidelines define the treatments based on grade and histologic type (**Table 2**).

Table 1. TNM and FIGO Staging Classifications for Ovarian Cancer

Primary tumor (T)		
TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the ovaries (1 or both)
T1a	IA	Tumor limited to 1 ovary; capsule intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
T1b	IB	Tumor involves both ovaries; capsules intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to 1 or both ovaries with any of the following: IC1 – surgical spill IC2 – capsule rupture before surgery or tumor on ovarian surface IC3 – malignant cells in the ascites or peritoneal washings
T2	II	Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim)
T2a	IIA	Extension and/or implant on the uterus and/or fallopian tube(s); no malignant cells in ascites or peritoneal washings
T2b	IIB	Extension to other pelvic intraperitoneal tissues; no malignant cells in ascites or peritoneal washings
T3	III	Tumor involves 1 or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
T3a	IIIA	Positive retroperitoneal lymph nodes and/or microscopic peritoneal metastasis beyond the pelvis (no macroscopic tumor) IIIA1 Positive retroperitoneal lymph nodes only IIIA1 (i) Metastasis ≤10 mm IIIA1 (ii) Metastasis >10 mm IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
T3b	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm in greatest dimension ± retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
T3c	IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm in greatest dimension ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen

(continued on page 9)

The subtypes of epithelial ovarian cancers are endometrioid, serous, mucinous, and clear cell, with Brenner's and squamous types composing less than 3%. Endometrioid is the most common malignant subtype, followed by serous and then mucinous and clear cell tumors (**Table 3**).⁷⁶ These subtypes as well as the low-grade serous tumors may be distinct from high-grade serous carcinoma and are classified as type I ovarian cancers. Type II carcinoma comprises the high-grade serous group (**Table 4**).⁷⁷ Also, clear cell and mucinous tumors

present more frequently at an earlier stage compared with serous tumors, and as an early stage can have a better prognosis.⁷⁸ Women presenting with stage IC disease are treated with chemotherapy given the poor prognosis compared with stage IA and IB disease, but it has been reported that if the stage IC is due to intraoperative rupture, the prognosis may be comparable to that of an earlier stage.⁷⁸ MD Anderson Cancer Center proposed a 2-tiered system for grading serous ovarian carcinoma that is based on the assessment of nuclear

Table 1. TNM and FIGO Staging Classifications for Ovarian Cancer (*continued*)

Regional lymph nodes (N)		
TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis
Distant metastasis (M)		
TNM	FIGO	
M0		No distant metastasis
M1	IV	Distant metastasis (excluding peritoneal metastasis) IVA Pleural effusion with positive cytology IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Notes:

- The presence of nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.
 - Liver capsule metastasis is T3/stage III; liver parenchymal metastasis, M1/stage IV. Pleural effusion must have positive cytology for M1/stage IV.
- Other major recommendations for FIGO staging are as follows:

Histologic type including grading should be designated at staging.

Primary site (ovary, fallopian tube or peritoneum) should be designated where possible.

Tumors that may otherwise qualify for stage I but are involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions.

Adapted with permission from Ovary and primary peritoneal carcinoma. In: Edge SB, Byrd DR, Compton CC, et al, eds. AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010:493–506; and Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 2014;124:15.

atypia with mitotic rate used as a secondary feature. The benefit would be to provide better reproducibility in the grading of serous ovarian tumors.⁸⁰

Observation

Treatment for IA and IB, grade 1 is surgical staging followed by observation. This group is considered potentially curable with surgery alone, with cure rates exceeding 90%.⁷⁵ For patients with grade 2 stage IA or IB disease, observation may be a consideration depending on the subtype as per the NCCN guidelines.

Adjuvant Systemic Chemotherapy

For stage IA and IB, grade 2, adjuvant chemotherapy with a platinum and taxane doublet is

recommended following optimal cytoreduction. In stage IA and IB, grade 3, stage IC or clear cell type, adjuvant chemotherapy is recommended after optimal surgical staging.

Early Gynecologic Oncology Group (GOG) trials validated the use of cisplatin-based chemotherapy.⁸¹ European groups also pursued this research, including Gruppo Interregionale Cooperativo Oncologico Gynecological (GICOOG) which compared cisplatin with a cisplatin-based regimen in advanced ovarian cancer; their finding suggested that cisplatin by itself was as effective as a platinum-based regimen.⁸²

Two large, randomized prospective phase 3 trials have demonstrated a benefit of using platinum-based regimens for adjuvant chemotherapy, the

Table 2. NCCN Practice Guidelines Findings/Primary Treatment (NCCN 1.2015 OV-2)

Stage	Findings	Primary Treatment
Suspected stage IA or IB, grade 1	–	Surgical staging
Suspected stage IA or IB, grade 2	If observation considered	Surgical staging
	Suspect residual disease	Completion surgery/surgical staging
	Suspect no residual disease	Completion surgery/surgical staging or chemotherapy for 6 cycles
Suspected stage IA or IB, grade 3 or clear cell or stage IC	Suspect residual disease	Completion surgery/surgical staging
	Suspect no residual disease	Completion surgery/surgical staging or chemotherapy for 6 cycles
Stage II, III, IV	Suspect potentially resectable residual disease	Tumor reductive surgery
	Suspect unresectable residual disease	Chemotherapy for a total of 6–8 cycles Consider completion surgery after 3 cycles followed by postoperative chemotherapy

Adapted from NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Including fallopian tube cancer and primary peritoneal cancer. Version 1.2015. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed March 5, 2015.

International Collaborative Ovarian Neoplasm trial 1 (ICON1) and the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial. These phase 3 trials randomly assigned postsurgical patients to either observation or platinum-based adjuvant chemotherapy. The ACTION trial enrolled 448 women with high-risk, early-stage disease (FIGO stage IA-IB, grade 2-3, all stage IC and IIA, and all stages I-IIA with a clear cell component).⁸³ Following cytoreductive surgery, patients were randomized to either observation or treatment with between 4 and 6 cycles of platinum-based therapy. After a median follow-up of 5.5 years, there was a statistically significant improvement in recurrence-free survival in the arm receiving adjuvant treatment (HR = 0.063, $P = 0.02$). ICON1 enrolled 477 early-stage patients, regardless of tumor grade. Patients were treated with 6 cycles of a platinum-based regimen.⁸⁴ After a median follow-up of 51 months, a statistically significant improvement in both OS (HR = 0.66, $P = 0.03$) and recurrence-free survival (HR = 0.45, $P = 0.03$) was observed. A combined analysis of these 2 in-

ternational studies suggested a significant benefit in 5-year OS in patients with higher-risk early-stage disease who are treated with adjuvant therapy, 74% versus 82% ($P = 0.008$), respectively.⁸³

Of note, although recommended, complete staging surgery with TAH, BSO, and omentectomy were not required for entry into the ICON1 trial, and taken in conjunction, these data suggest a beneficial role for the use of platinum-based adjuvant therapy, with the ACTION trial demonstrating the greatest benefit in those women who had suboptimal surgery, and thus more advanced disease. The 10-year follow-up in the ICON1 study has maintained significance for recurrence-free survival (HR = 0.69; $P = 0.02$) and overall survival (HR = 0.71; $P = 0.04$).⁸⁵

Additional studies concerning adjuvant chemotherapy in early-stage disease have addressed the question of how many cycles of platinum-based therapy should be administered. GOG conducted a randomized phase 3 trial (GOG 157) that enrolled 427 patients who received either 3 or 6 cycles of adjuvant carboplatin/paclitaxel.⁸⁶ These

Table 3. Subtypes of Epithelial Ovarian Malignancies

	Cancer Type					
	Serous	Mucinous	Endometrioid	Clear Cell	Brenner's	Squamous
Malignant frequency (%)	36	5	77	3	1	3 (Mixed) 2 (Undifferentiated)

Adapted from Ozols RF, Rubin SC, Thomas GM, Robboy SJ. Epithelial ovarian cancer. In: Hoskins WJ, ed. Principles and practice of gynecologic oncology. Philadelphia: Lippincott Williams & Wilkins; 2005:904.

results indicated a trend towards a lowered recurrence risk with 6 cycles of treatment (HR = 0.761, $P = 0.18$). No difference in OS was observed. In comparing 3 cycles versus 6 cycles, grade 3 or 4 neurotoxicity was significantly increased from 2% to 11%, respectively, and there was more anemia and granulocytopenia in those patients receiving 6 cycles. This study was updated in 2010 for subgroup analysis, and a lower risk of recurrence was noted in the serous group having 6 cycles (HR = 0.33, $P = 0.04$). The findings also noted a 5-year recurrence-free survival advantage for 6 cycles (83%) versus 3 cycles (60%) in those with serous tumors ($P = 0.007$).⁸⁷

GOG 175 evaluated the recurrence-free interval (RFI) and safety profile in 542 patients with fully resected high-risk early stage ovarian cancer patients treated with intravenous carboplatin and paclitaxel with or without maintenance low-dose paclitaxel for 24 weeks.⁸⁸ Patients with stage I-A/B (grade 3 or clear cell), all IC, or stage II disease were included. All patients received carboplatin AUC 6 and paclitaxel 175 mg/m² every 3 weeks for 3 courses, with randomization to either observation or maintenance paclitaxel 40 mg/m²/week for 24 weeks. Three cycles were completed by 97% and 80% of those assigned to maintenance completed the regimen. Within the maintenance group, peripheral neuropathy (15.5%), infection/fever (19.9%), and skin reactions (70.8%) were noted at grade 2 or worse. The probability of sur-

vival at 5 years was 85.4% for patients on maintenance paclitaxel and 86.2% for those patients in surveillance. The conclusion was that maintenance paclitaxel added to standard-dose carboplatin and paclitaxel showed no significant increase in RFI.⁸⁸

These studies of adjuvant chemotherapy in early-stage disease are summarized in **Table 5**.

Adjuvant radiation therapy has also been investigated, but few randomized trials are available, and its use as adjuvant therapy in ovarian cancer is not commonly practiced.

STAGE II

For stage II disease following optimal cytoreduction to no gross residual, recommended treatment is either standard chemotherapy with a taxane and platinum agent given every 3 weeks or intraperitoneal chemotherapy.²⁶

CASE PATIENT CONTINUED

The patient recuperates from surgery and, given her stage which was defined by the capsular rupture, chemotherapy with paclitaxel and carboplatin is recommended. The data on 3 versus 6 cycles of treatment is reviewed with her, and since she is not considered high risk by subtype (not pap serous or clear cell type) but did have evidence of extensive endometriosis, her physicians elect to treat for 6 cycles total. Her treatment course is unremarkable since she is very compliant with prescribed anti-nausea medications, maintains good oral hydration

Table 4. Summary of Subtype Characteristics

Characteristics	HGSC	LGSC	MC	EC	CCC
Risk factors	BRCA1/2	?	?	HNPCC	?
Precursor lesions	TIC	Serous borderline tumor	Cystadenoma/ borderline tumor	Atypical endometriosis	Atypical endometriosis
Patterns of spread	Very early Transcoelomic	Transcoelomic	Usually confined to ovary	Usually confined to pelvis	Usually confined to pelvis
Molecular abnormalities	BRCA P53	BRAF KRAS	KRAS HER2	PTEN ARIDIA	HNF1 ARIDIA
Chemosensitivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

CCC = clear cell carcinoma; EC = endometrioid carcinoma; HGSC = high-grade serous carcinoma; LGSC = low-grade serous carcinoma; MC = mucinous carcinoma; TIC = tubal intraepithelial carcinoma.

Adapted with permission from Prat J. New insights into ovarian cancer pathology. *Ann Oncol* 2012; 23(suppl 10):111–17.

and nutrition, and tries to keep an active lifestyle. Her first CA-125 pre-cycle 1 was 100 U/mL and after 3 cycles the marker drops to 20 U/mL. At the completion of the course, the marker is 10 U/mL. She has not experienced neuropathy and her CBC was maintained throughout the course without the need for growth factor support.

• **Is there a role for maintenance chemotherapy?**

There are no phase 3 studies defining maintenance chemotherapy as a treatment modality in early-stage disease.

• **How should the patient be monitored for disease recurrence?**

SURVEILLANCE

For patients who achieve clinical response following adjuvant chemotherapy, surveillance is typically conducted every 3 months and consists of history and physical examinations (pelvic examination minimum of twice per year) and monitoring CA-125 levels.

An early study examining the correlation of CA-125 levels with disease progression found the CA-125 to be elevated in 73% of patients at the time of progression, with elevation of CA-125 levels occurring before clinical progression in 63% of all patients.⁸⁹ In patients who had elevated CA-125 levels before clinical progression, the median lag time was 4.5 months (range 0.5–29.5 months).

The Gynaecologic Cancer Intergroup (GCIG) has proposed a set of criteria, based upon the CA-125 level in conjunction with standard RECIST (Response Evaluation Criteria in Solid Tumors) criteria, to evaluate clinical response and progression in clinical trials conducted by its participating groups.⁹⁰ Specifically, the GCIG/RECIST criteria for disease response is a 50% reduction in CA-125 levels that is maintained for 28 days. The GCIG/RECIST criteria for disease progression are dependent on the patient’s CA-125 level prior to treatment. For patients with an initially elevated CA-125 level that normalized following treatment or for patients who had a normal CA-125 level, progression is defined as a CA-125 level 2 times greater than

Table 5. Studies of Adjuvant Chemotherapy in Early-Stage Epithelial Ovarian Cancer

Trial	Treatment	Outcomes
GOG 157 Bell et al 2006 ⁸⁶	Paclitaxel/carboplatin 3 vs 6 cycles	5-yr DFS for 3 vs 6 cycles was 75% and 80% 5-yr OS for 3 vs 6 cycles was 81% and 83%
GOG 157 Chan et al 2010 ⁸⁷	Subgroup analysis	5-yr DFS for 3 vs 6 cycles were 60% and 83% (<i>P</i> = 0.007) Hazard ratio for serous tumor having 6 cycles = 0.33 (<i>P</i> = 0.04)
GOG 175 Mannel et al 2011 ⁸⁸	Paclitaxel/carboplatin for 3 cycles in both arms, then weekly paclitaxel for 24 wk vs observation	5-yr survival of 85.4% for maintenance paclitaxel vs 86.2% for observation

DFS = disease-free survival; OS = overall survival.

Adapted from Tangjitgamol S, Kavanagh, J. Cytotoxic trials by the Gynecologic Oncology Group. <http://www.esgo.org/Education/PublishingImages/131.pdf>. Accessed March 5, 2015.

the upper limit of normal on 2 occasions separated by at least 1 week. For patients with initially elevated levels of CA-125 that did not normalize following treatment, progression is defined as a CA-125 level 2 times greater than the nadir following treatment. In patients with suspected recurrence, a CT scan should also be considered to assess for the presence of visible disease. However, the sensitivity of CT in some studies has been shown to be as low as 40%, and the use of positron-emission tomography/CT has shown high sensitivity and positive predictive value in diagnosing macroscopic recurrent disease in the setting of equivocal findings on conventional CT.⁹¹

CASE PATIENT CONCLUSION

After completing chemotherapy, the patient begins the routine alternating schedule of follow-up between gynecologic surgery and medical oncology every 3 months for 2 years and then every 6 months for a total of 5 years, with the CA-125 checked at each visit. She also sees a genetics specialist as recommended by the NCCN guidelines, and *BRCA* testing is negative for mutation. At the completion of her 5 years of follow-up, her CA-125 remains at 22 U/mL and she is without gastrointestinal or pelvic

symptoms. She is then referred back to her local gynecologist for long-term follow-up.

CONCLUSION

Based on early clinical trials, the benefit of surgery and chemotherapy has been established in the management of ovarian carcinoma. In addition to this standard, the issues of screening and maintenance are topics still undergoing study.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic.
Go to www.turner-white.com and select Oncology from the drop-down menu of specialties.

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