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## Ovarian Cancer Tests and Treatment

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### Abstract

Lack of symptoms in early-stage ovarian cancer leads to a high mortality rate overall. Tests and therapy are discussed here, along with the symptom index.

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Ovarian cancer is the 5th most frequent cause of death from cancer in women in the United States.<sup>1</sup> More than 70% of cases are diagnosed with advanced disease because of the lack of specific symptoms in early stage. Survival rates for early-stage disease are greater than 90%; survival is less than 30% in advanced stage.

Women with the highest risk for ovarian cancer include those with hereditary breast-ovarian cancer syndrome with *BRCA* gene mutation. Women at high risk for hereditary breast-ovarian cancer syndromes can be identified by risk assessment for personal and family history of breast and ovarian cancer. Ovarian cancer risk is decreased in multiparous women and those who have breastfed, have had a tubal ligation or hysterectomy, or have been on oral contraceptive pills for at least 5 years.

### DIAGNOSIS OF OVARIAN CANCER

Ovarian cancer is rarely diagnosed based on symptoms during the early stage. However, a constellation of symptoms may be associated with ovarian cancer, including pelvic or abdominal pain, abdominal swelling or bloating, and difficulty eating or feeling full. When these 6 symptoms are included in a symptom index, any 1 of the symptoms present on more than 12 days per month for up to 1 year is associated with ovarian cancer with a 56.7% sensitivity for early-stage disease, 79.5% sensitivity for advanced-stage disease, 90% specificity for women older than 50, and 86.7% specificity for women younger than 50.<sup>2</sup>

The most commonly used tests for the detection of ovarian cancer include transvaginal ultrasound (TVS) and serum CA-125. When used to evaluate the adnexa, TVS has an 85% sensitivity and 98% specificity to differentiate benign from malignant masses in low-risk postmenopausal women.<sup>3</sup> CA-125 is elevated in approximately 80% of women who have malignancies and in approximately 20% of women with benign disease. These 2 modalities have been studied together in several investigations.

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The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial was a randomized controlled study of women ages 55 to 74 that showed the positive predictive value for invasive cancer was 3.7% for abnormal CA-125 alone, 1.0% for abnormal TVS alone, and 23.5% if both tests were abnormal.<sup>4</sup>

The UK Collaborative Trial of Ovarian Cancer Screening studied postmenopausal women at low risk for ovarian cancer who were screened with CA-125 and subsequent TVS for abnormal serum values, with a specificity of 99.8% and a positive predictive value of 35.1% for invasive cancer.<sup>3</sup>

There is no consensus about whether the general population should be screened for ovarian cancer, since studies do not show a reduction in mortality with screening. ACOG currently does not recommend population-based screening for ovarian cancer. It has advised that the best method of detection for early ovarian cancer is for both the patient and physician to have a high index of suspicion.<sup>5</sup>

Data are emerging about new biochemical markers that may increase the positive predictive value of screening for ovarian cancer. The symptom index described above, CA-125, and serum HE4 used in combination have a sensitivity of 84% and a specificity of 98.5% when 2 of the 3 are positive.<sup>6</sup> In addition, a panel using the combination of biomarkers CA-125, HE4, CEA, and VCAM-1 has an 86% sensitivity and a 98% specificity in healthy women.<sup>7</sup>

In September 2009, FDA approved the OVA1™ Ovarian Triage Test, which measures the serum levels of 5 potential biochemical markers for ovarian cancer (transthyretin, apolipoprotein A1,  $\beta$ 2-microglobulin, transferrin, and CA-125). It uses a multimarker algorithm to determine whether women with ovarian tumors who are planning to undergo surgery are at high risk to have a malignancy, with the goal to triage women who should be referred to a gynecologic oncologist for surgery.

Vermillion, Inc, developed the test in conjunction with Quest Diagnostics, and they reported a >90% sensitivity and 90% negative predictive value in a preoperative population of premenopausal and postmenopausal women.<sup>8</sup>

Unfortunately, little scientific data are available to support the clinical benefits of OVA1 or other tests of biochemical markers for the screening or detection of ovarian cancer. OVA1 can be utilized as a tool for appropriate referral to a gynecologic oncologist; however, care should be taken to use and interpret this test correctly. OVA1 should not be used independently of clinical assessment.

A negative OVA1 result should not negate a referral, if clinical assessment alone would indicate a referral for malignancy. OVA1 is not needed when clinical assessment favors conservative management. Also, it should not be used as a screening test in a woman without an adnexal mass.<sup>9</sup> In order to show the utility of a test for screening purposes, very large studies would be required because of the low prevalence of ovarian cancer in the general population.

## TREATMENT OF OVARIAN CANCER

Ovarian cancer is typically treated by primary surgical resection with complete surgical staging (including dissection of the pelvic and para-aortic lymph nodes, omentectomy, and peritoneal and diaphragm biopsies). Adjuvant treatment with chemotherapy is given, except in the earliest stage (Table).<sup>10</sup> When optimal cytoreductive surgery (<1 cm residual disease) is not deemed feasible preoperatively, or if a patient is not medically stable for surgery,

treatment may be initiated with neoadjuvant chemotherapy and interval cytoreductive surgery.

Early-stage ovarian cancer (with the exception of stage IA or stage IB with grade 1 or 2) is treated with adjuvant chemotherapy with a platinum- and taxane-based regimen. This can be given for 3 or 6 cycles with similar overall survival; however, there is a higher risk of recurrence after only 3 cycles.<sup>11</sup> Recently, adjuvant treatment with 3 cycles of carboplatin and paclitaxel versus 3 cycles plus an additional 24 weeks of maintenance therapy with low-dose weekly paclitaxel in early-stage disease has suggested that maintenance therapy is safe in this population but does not increase overall or progression-free survival.<sup>12</sup>

Advanced-stage ovarian cancer is treated with 6 cycles of adjuvant platinum and taxane therapy. In 2006, the results of the GOG 172 trial showed that treatment with intraperitoneal (IP) cisplatin in combination with intravenous (IV) paclitaxel resulted in a 16-month improvement in median overall survival in patients who have had optimal cytoreduction of stage III ovarian cancer.<sup>13</sup>

Although IP chemotherapy is associated with significant toxicities, with only 42% of women in the study able to complete 6 cycles, the National Cancer Institute issued a statement recommending IP chemotherapy as the standard of care for appropriate patients. Many groups have attempted to alter the regimen to reduce toxicity and intolerability while maintaining efficacy.

Treatment with targeted therapies in which the abnormal growth pathways of cancer cells are inhibited has been under investigation. Bevacizumab inhibits angiogenesis by binding to vascular endothelial growth factor A and has been shown to be effective in recurrent ovarian cancer, when used alone, in combination with oral cyclophosphamide, or in conjunction with taxanes. Its role in upfront therapy in the GOG 218 trial was recently presented and showed a significant increase in progression-free survival by 3.8 months when bevacizumab is used in conjunction with carboplatin and paclitaxel for 6 cycles plus an additional 16 cycles of maintenance therapy with bevacizumab, compared to the standard 6 cycles of carboplatin plus paclitaxel.<sup>14</sup> The 5-year overall survival data have not yet been reported. Consensus has not been established regarding the incorporation of bevacizumab into standard upfront therapy for advanced epithelial ovarian cancer.

## SUMMARY

Women who are diagnosed with ovarian cancer have an overall survival rate of 30%. Ovarian cancer is often diagnosed in advanced stage because of the lack of specific symptoms associated with early-stage disease. A symptom index which incorporates a constellation of patient complaints including pelvic or abdominal pain, abdominal swelling or bloating, and difficulty eating or feeling full may be predictive of ovarian cancer.

The combination of TVS and serum CA-125 levels is commonly used for the detection of ovarian cancer and has a 23% to 35% positive predictive value for invasive cancer. Several new tests of biochemical markers have been developed; however, none are associated with data to support the clinical benefit of their use in the screening or detection of ovarian cancer.

Ovarian cancer is generally treated by initial surgical resection followed by adjuvant systemic chemotherapy in all but the earliest stage. Upfront chemotherapy is a combined platinum- and taxane-based regimen. In patients with optimally debulked advanced-stage epithelial ovarian cancer, chemotherapy is often given intraperitoneally and intravenously.

Bevacizumab is being used more frequently in the recurrent setting, and promising new data may encourage its use in upfront chemotherapy regimens in the future.

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**FOCUSPOINT**

The most commonly used tests for the detection of ovarian cancer include transvaginal ultrasound (TVS) and serum CA-125.

Ovarian cancer is often diagnosed in advanced stage because of the lack of specific symptoms associated with early-stage disease.

TABLE

FIGO Staging for Carcinoma of the Ovary<sup>10</sup>

<b>Stage I</b>	Growth limited to the ovaries.
<b>IA</b>	Growth limited to 1 ovary, no ascites present containing malignant cells. No tumor on the external surface; capsule intact.
<b>IB</b>	Growth limited to both ovaries, no ascites; present containing malignant cells. No tumor on the external surface; capsule intact.
<b>IC</b>	Tumor classified as either stage IA or IB but with tumor on the surface of 1 or both ovaries; or with ruptured capsule(s); or with ascites containing malignant cells or with positive peritoneal washings.
<b>Stage II</b>	Growth involving 1 or both ovaries, with pelvic extension.
<b>IIA</b>	Extension and/or metastases to the uterus and/or tubes.
<b>IIB</b>	Extension to other pelvic tissues.
<b>IIC</b>	Tumor either stage IIA or IIB but with tumor on the surface of 1 or both ovaries; or with capsule(s) ruptured; or with ascites containing malignant cells or with positive peritoneal washings.
<b>Stage III</b>	Tumor involving 1 or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.
<b>IIIA</b>	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of the abdominal peritoneal surfaces.
<b>IIIB</b>	Tumor of 1 or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative.
<b>IIIC</b>	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
<b>Stage IV</b>	Growth involving 1 or both ovaries, with distant metastases. If pleural effusion is present, there must be positive cytology findings to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.