Primary care considerations for women with an identified pelvic mass

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Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Describe the initial assessment components in a primary care setting for women with an identified pelvic mass.
2. Discuss the appropriate use and interpretation of serum tumor biomarkers for risk assessment of ovarian malignancy.
3. Discuss criteria indicating the need to refer the patient with a pelvic mass to a gynecologic oncologist.

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Evaluation of adnexal or pelvic masses for malignancy can be challenging in the primary care setting. Noninvasive presurgical considerations for clinical evaluation include serum CA125, HE4, and OVA1. Emerging evidence indicates ethnic disparities exist in CA125 threshold levels. Multivariate assays may help inform the primary care clinician of malignancy risk for all histologic subtypes of ovarian cancer and improve referral patterns to gynecologic oncology settings.

KEY WORDS: **adnexal mass, ovarian cancer, ovarian malignancy, CA125, HE4, OVA1, multivariate assay**

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Ovarian cancer is the deadliest gynecologic cancer and the fifth leading cause of cancer-related death for women in the United States. It is most frequently diagnosed among women age 55 to 64 years.[1] In 2022, 19,880 new cases of ovarian cancer were diagnosed and 12,810 women died from ovarian cancer.[1] Early detection of ovarian cancer is clinically important as metastasis is common and prognosis is directly dependent on stage at time of diagnosis. When detected at an early stage, the 5-year survival rate is greater than 90%. However, 80% of ovarian cancer cases are detected at an advanced stage when the 5-year relative survival rate is 30%.[1] The majority of patients with undetected ovarian cancer will initially present in a primary care setting. The ability to properly assess the risk for an ovarian malignancy can improve early diagnosis and appropriate referral to a gynecologic oncology specialist, which is paramount to improve survival rates. This article describes assessment and referral considerations for clinicians in a primary care setting when a pelvic or adnexal mass has been detected.

Clinical detection

Clinical detection of ovarian cancer is challenging. Early stages are asymptomatic, and all screening methods have proven to be ineffective. Risk factors have been identified (*Table 1*).[2] Yet ovarian cancer can occur in any woman even in the absence of risk factors.

Symptoms in advanced stages are nonspecific and can be generalized to other conditions. No strategy for early detection of ovarian cancer is currently recommended.[3] Most women are diagnosed after symptom onset. Clinicians should consider ovarian cancer on a differential diagnosis if signs or symptoms outlined in *Table 2* are of new onset and manifest for more than 12 days in a month.[3,4]

The presence of a pelvic or adnexal mass identified through physical exam or as an incidental finding on imaging for another reason is of potential concern. Pelvic and adnexal masses are common and statistically likely to be of benign origin, but clinical evaluation is warranted to rule out potential malignancy.[3] The initial physical examination should include palpation of cervical, supraclavicular, axillary, and groin lymph nodes; pulmonary auscultation; abdominal palpation and auscultation; pelvic examination with visual inspection of the perineum, cervix, and vagina and bimanual palpation; and a rectovaginal examination if indicated.[5] The presence of a palpable pelvic mass that is irregular, firm, fixed, nodular, bilateral, or associated with ascites or abdominal distention is concerning for malignancy.[5] A nutritional status assessment also should be conducted. Clinicians should obtain a comprehensive family cancer history and refer for genetic counseling as indicated.[6] It is important to note that primary treatment for suspected ovarian malignancy should never be delayed while awaiting genetic counseling.

Transvaginal ultrasound is recommended for initial diagnostic evaluation when a mass is identified on a pelvic exam.[3] Characteristics for concern on adnexal imaging are listed in *Table 3*.[5] If first-line imaging is indeterminate or indicates concern for metastatic disease, clinicians should use further diagnostic imaging. Contrast-enhanced computed tomography (CT) of the abdomen and pelvis may be helpful in evaluating metastasis, but it is not intended to detect

Table 1. Risk factors for ovarian cancer[2]

- Family history of breast or ovarian cancer in first–degree relative
- Mid–life or older (median age, 63 years)
- Mutations in *BRCA1* and *BRCA2* genes
- Lynch syndrome and related mismatch repair cancer syndrome
- Personal history of breast, uterine, or colorectal cancer
- Eastern European or Ashkenazi Jewish background
- Polycystic ovary syndrome
- Endometriosis
- Obesity
- Nulliparity
- Unsuccessful infertility treatment (ovarian hyperstimulation)

Note: Ovarian cancer can occur in any woman even in the absence of risk factors.

Table 2. Signs and symptoms of ovarian cancer[4]

Most commonly reported
- Bloating or abdominal distension
- Pelvic or abdominal pain
- Early satiety or loss of appetite
- Urinary urgency or frequency

Occur less frequently
- Postmenopausal vaginal bleeding
- Rectal bleeding
- Weight loss

Table 3. Characteristics for concern on adnexal mass imaging[5]

- Cyst > 10 cm
- Papillary or solid components
- Irregularity
- Presence of ascites
- High color Doppler flow

or characterize a mass and should not be used as a front-line modality.[5] If CT is unavailable, a chest x-ray for women with respiratory symptoms may be helpful for evaluation of the thorax.[7] In maximal-sourced settings, pelvic magnetic resonance imaging with contrast is recommended when first-line imaging is indeterminate.[7] Diagnostic laboratory workup includes a complete blood count, a blood chemistry including liver function tests, and serum cancer antigen 125 (CA125) in the postmenopausal patient.[6] If indicated from nutritional status, serum protein, albumin, and transferrin may be appropriate.[6]

The definitive diagnosis for ovarian cancer occurs through histologic exam, often following surgery. Biopsies are generally avoided due to risk of spillage and seeding of malignant cells.[8] When high clinician suspicion for a malignant or borderline ovarian tumor occurs, referral to a gynecologic oncology specialist is recommended. Five-year survival rates are highest when initial surgical intervention and staging is performed by an experienced gynecologic oncologist as compared to a general gynecologist.[9] However, research indicates less than 50% of patients with confirmed ovarian cancer had initial surgical management performed by a gynecologic oncologist. Location can be a barrier to care, especially in areas geographically distant from tertiary academic centers, which account for 73% of gynecologic oncology practice.[10] Other identified barriers to access include under-developed referral networks and insurance-based disparities. A significant number of community health centers are unaffiliated with specialty care centers and at risk for treatment delays when referrals are indicated.[11] Medicare Advantage plans do not include access to a gynecologic oncologist as a network adequacy standard, while Medicaid and commercial plans are under no legal requirement to provide in-network access to a gynecologic oncologist.[11] The Centers for Disease Control and Prevention (CDC) has identified access to subspecialty care for ovarian cancer as a priority to improve ovarian cancer survival. Recommended mitigation strategies for patient, provider, and system level factors are outlined in the CDC's Toolkit to Increase Receipt of Ovarian Cancer Care from a Gynecologic Oncologist, available online.[12]

Presurgical identification of malignancy remains difficult, especially in lower-sourced settings, with premenopausal women, and in early stages of the disease. Many of the guidelines for care have been based on maximally sourced settings with imaging conducted by experienced ultrasonographers in specialty care centers. This level of experience is not available in all settings. When used in conjunction with imaging, serum biomarkers may assist the primary care clinician with categorizing the mass for risk of malignancy.

CA125

Serum cancer antigen 125 is the most frequently used tumor marker for the early assessment for ovarian malignancy. Despite widespread use, challenges are seen with the reliance on CA125 for early detection. CA125 has a low sensitivity and specificity for the detection of ovarian cancer. Elevated CA125 levels occur in less than 50% of early-stage ovarian cancer and 75% to 80% of advanced-stage ovarian cancer.[5] CA125 elevation varies widely based on histology. CA125 is overexpressed in serous epithelial ovarian cancer, which accounts for 70% of ovarian malignancies.[13] However, many other histologic subtypes of ovarian cancer can occur. Some of the less common ovarian cancers, malignant germ cell tumors, malignant sex cord-stromal tumors, clear cell carcinomas, undifferentiated carcinomas, and or mucinous carcinomas rarely exhibit CA125 elevation.[5,13] Menopause has a significant impact on baseline CA125 expression. The levels of CA125 are substantially higher in premenopausal women as compared to postmenopausal women.[5] Many common benign conditions also elevate CA125, including endometriosis, uterine leiomyomas, pelvic inflammatory disease, systemic lupus erythematosus, inflammatory bowel disease, pregnancy, and use of hormone therapy for menopausal symptom management.[5,9]

The reliance on CA125 for early ovarian cancer detection is especially concerning given the ethnic disparities in clinical performance. Emerging evidence indicates that race is the biggest predictor of CA125 levels.[14–18] Several studies

indicate that CA125 levels vary based on ethnicity. African American and Asian women display CA125 levels 13% to 24% lower than White women, while women with Jewish ancestries have higher CA125 elevations than other women with the same histologic ovarian cancer type.[14–18] Clinicians should use caution when interpreting CA125 levels to establish oncology referral need, especially if the threshold is not individualized.

HE4

Human epididymis protein (HE4) is another frequently used biomarker for the risk assessment of ovarian malignancy. Unlike CA125, HE4 levels are not affected by pregnancy, menstrual cycle, hormone treatment, or endometriosis.[9] HE4 levels may be elevated, however, in current smokers or in patients using oral contraceptives. When added to diagnostic workup, HE4 with CA125 outperforms CA125 alone for early-stage detection. The addition of HE4 to prediction algorithms has significantly improved referral patterns, decreasing the number of benign referrals to a gynecologic oncology setting and increasing the number of malignant referrals to specialty care.[19] Similar to CA125, HE4 expression varies based on histology type and increases in HE4 have not been observed in all types of ovarian cancer.[13] HE4 frequently appears in clinical guidelines but is not as widely recommended as CA125, leading to variable levels of insurance coverage or the need for prior authorization.

Multivariate index assays

One of the challenges of presurgical risk assessment for ovarian cancer is the potential for a number of different biomarker patterns based on histologic subtype. A single biomarker is unlikely to adequately assess the risk for all women suspected of ovarian malignancy. OVA1® was the first FDA-approved multivariate assay of seven biomarkers selected to target all histologic expressions of ovarian cancer: apolipoprotein, beta-2 microglobulin, prealbumin, transferrin, follicle-stimulating hormone, HE4, and CA125. It was developed for the nongynecologic oncologist to predict risk of malignancy and is ideal for use in low-resourced settings and geographically remote areas. This send-out laboratory test uses a proprietary testing kit from a single blood draw, with a turnaround time of 72 hours. It is accepted on many commercial, Medicare, and Medicaid plans.

OVA1 has a high sensitivity for the detection of ovarian cancer (96%) and accuracy with predicting absence of malignancy, with a negative predictive value of 98%.[20] It performs well (91.3%) in the assessment of early-stage ovarian cancer compared to CA125 (65.7%) and outperforms CA125 in the detection of ovarian cancer in premenopausal women (46% vs 91%). It also outperforms CA125 and HE4 in detecting ovarian cancer in African American women.[21] The use of OVA1 has improved referral patterns of the patient with an adnexal mass. Elevated OVA1 scores are more likely to be referred to a gynecologic oncologist, whereas low-risk scores are more likely to have care managed in a general gynecology setting.[22]

Two other multivariate assays are now FDA approved. The Centers for Medicare and Medicaid Services website has information on all three tests, including a summary of evidence on prognostic performance.[23]

> The evidence is clear that patients with suspected ovarian cancer who are referred to gynecologic oncology experience better outcomes and improved survivability.

When to refer or retain the patient with an adnexal mass

In general, clinicians should refer all patients with an identified adnexal mass and:

- Postmenopausal with CA125 elevation over 30 U/mL, ultrasound suggestive of malignancy, ascites, nodular or fixed pelvic mass, or evidence of metastasis[5]
- Premenopausal with CA125 elevation greater than 200 U/mL, ultrasound suggestive of malignancy, ascites, nodular or fixed pelvic mass, or evidence of metastasis[5]
- Pre- or postmenopausal with elevated score on the OVA1 multivariate assay formal risk assessment[5]

Referral to a gynecologic oncologist may not be appropriate or necessary in cases with low risk for malignancy.[5] Expectant management is appropriate when imaging suggests the mass is benign.[5] No ideal follow-up interval has been recommended for a benign adnexal mass. It may be prudent to conduct short interval imaging in 1 to 3 months as evidence indicates that malignant growth is likely to be identified by 7 months.[5] After a mass is determined

Box. Additional practice resources

- Centers for Disease Control and Prevention. Action Plan to Increase Receipt of Ovarian Cancer Care from Gynecologic Oncologists. cdc.gov/cancer/ovarian/gynecologic-oncologist/pdf/ovarian-cancer-action-plan-v2-508.pdf[B]
- Gilligan T, Coyle N, Frankel RM, et al. Patient-clinical communication: American Society of Clinical Oncology Consensus Guideline. *J Clin Oncol.* 2017;35(31):3618-3634. ascopubs.org/doi/pdf/10.1200/JCO.2017.75.2311[C]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, 2023. nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf[D]
- Patient resource: American Society of Cancer Oncology. Cancer.Net: Ovarian, Fallopian Tube, and Peritoneal Cancer. cancer.net/cancer-types/ovarian-fallopian-tube-and-peritoneal-cancer[E]

to be stable, interval imaging may occur on an annual basis depending on characteristics of the mass.[5]

Implications for practice

Primary care remains the most likely point of entry for a patient with an undetected ovarian malignancy. Providers should be attentive to any patient reporting abdominal or pelvic pain, bloating or abdominal distension, and gastrointestinal concerns. Women with ovarian cancer experience these symptoms more frequently than the general population. The initial evaluation should include a comprehensive family cancer history, a focused abdominal and pelvic exam, and an assessment of nutritional status. Transvaginal ultrasound is the first-line imaging modality for evaluation of an identified or suspected adnexal mass. The gold standard for diagnosis is a histologic exam by an experienced gynecologic oncologist. The evidence is clear that patients with suspected ovarian cancer who are referred to gynecologic oncology experience better outcomes and improved survivability, but access to subspecialty care remains a barrier and many primary care clinicians serve patients vulnerable to delays in diagnosis and treatment. Telehealth is not an appropriate option for the patient with an adnexal mass who needs expert imaging and specialty surgery for diagnosis, staging, and treatment. The ability to rapidly refine presurgical malignancy risk prediction is paramount to identifying the need for specialty care against expectant local management. Clinicians should use extreme caution, with reliance on CA125 in premenopausal women, women with conditions that elevate the serum levels, and in non-White populations. The Ova1 multivariate assay offers superior risk assessment for ovarian cancer in premenopausal women, in early-stage cancers, and in non-White populations and is an affordable option for determining malignancy risk in settings where access to gynecologic oncology is scarce. The *Box* provides additional resources for building referral networks, holding crucial conversations with patients, conducting high-risk cancer assessments, and online resources for patients.

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