Management of the Adnexal Mass

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Adnexal masses are commonly encountered in gynecologic practice and often present both diagnostic and management challenges. This is partly because of the fact that the majority of adnexal masses that are identified represent benign entities that do not necessarily require active intervention, yet a small subset will represent malignant processes that require both timely and appropriate surgical intervention for optimal outcome. To determine the best diagnostic and management strategies in this setting, physicians must effectively triage risk for malignancy by having a thorough understanding of the entities on the differential diagnosis and carefully considering the clinical context for each individual patient. Optimal selection and interpretation of diagnostic tests are enhanced by both an accurate clinical risk assessment and an understanding of the inherent accuracy of diagnostic tests considered in this setting. The purpose of this document is to provide clinicians with a practical strategy for distinguishing benign and malignant masses in the nonpregnant woman. Our approach addresses the critical elements of accurate risk stratification, reviews the performance of diagnostic tests for identifying malignancy, and offers evidence-based management algorithms to optimize outcomes for women with adnexal masses.

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Ovarian cancer is the most lethal of the gynecologic malignancies, with an overall 5-year survival rate of less than 40%.[1] The high mortality rate has been attributed to an inability to detect ovarian cancer during its early stages; however, this mortality rate varies substantially according to the histologic features of the tumor. These sobering statistics have led to efforts to develop approaches for the early detection of ovarian cancer in hopes of reducing the morbidity and mortality.[2]

Generally, if an adnexal mass is considered to have an appreciable risk for representing a malignancy, then surgery is indicated. However, adnexal masses are a common finding among women and often present both diagnostic and management challenges because the majority represent benign or nonmalignant entities that do not necessarily require active surgical intervention. To determine the most appropriate diagnostic and management strategy for the woman identified to have an adnexal mass, physicians must effectively triage risk for malignancy by carefully considering the clinical context for each individual patient.

At this time, there are no accepted effective screening tests to identify women with ovarian cancer, partly because of the low prevalence of ovarian cancer in the general population[3] and the inherent biology of the cancer.[4,5] In the absence of effective screening tools, adnexal masses may be detected by the annual pelvic examination, during a work-up of women presenting with symptoms, or as an incidental finding on imaging studies obtained as part of a diagnostic work-up for an unrelated health condition.

Why should we make a major effort to discriminate benign from malignant masses? For women with significant symptoms in whom surgery may be appropriate, the principal reason is to facilitate referral to clinicians who have specialized training in managing

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ovarian cancer. For asymptomatic or minimally symptomatic women, discriminating benign from malignant disease will enable appropriate and timely management and avoid needless diagnostic procedures.[2]

CLINICAL RELEVANCE

Adnexal masses are a common finding among both premenopausal and postmenopausal women, and yet an accepted definition for what constitutes an adnexal mass does not exist. Partly for this reason, accurate statistics on their incidence are not available; however, nearly 10% of women at some point in their lives will undergo surgical evaluation for an adnexal mass or a suspected ovarian neoplasm,[6,7] resulting in an estimated 60,000 surgical excisions in the United States per year.[6] The majority of adnexal masses prevalent in the population, however, are benign, with only a small percentage of patients harboring an ovarian malignancy. Whereas one of the main goals of the initial diagnostic evaluation for the adnexal mass is to exclude malignancy, a closely related goal is to differentiate the adnexal masses that require active surgical intervention from those more appropriately managed medically or observed.

CLASSIFICATION AND CLINICAL PERSPECTIVE

The differential diagnosis of the adnexal mass includes both gynecologic and nongynecologic entities. Of the gynecologic sources, diagnostic entities can be broadly separated into functional or physiologic, inflammatory, or neoplastic (Box 1).

Box 1. The Adnexal Mass: The Most Common Etiologies

Functional or Physiologic
- Follicles
- Hemorrhagic
- Corpus luteum

Inflammatory
- Pelvic inflammatory disease
- Endometrioma

Other Benign
- Paratubal cysts
- Hydrosalpinx
- Ectopic pregnancy
- Ovarian torsion

Benign Neoplasms
- Germ cell
  - Mature cystic teratoma
- Sex cord stromal
  - Fibroma
- Epithelial
  - Serous or mucinous cystadenoma

Malignant Neoplasms
- Germ cell tumor
  - Dysgerminoma
  - Immature teratoma
- Sex cord stromal tumor
  - Granulosa cell tumor
  - Epithelial ovarian carcinoma
- Borderline or low malignant potential
  - Invasive epithelial
  - Fallopian tube carcinoma

Functional ovarian cysts arise from an unruptured follicle or from the cystic degeneration of the corpus luteum, ultimately undergoing atresia or involution. Occasionally, a hemorrhagic cyst develops and may evolve slowly into various stages of acute hemorrhage, clot formation, and clot retraction, thus giving rise to changing sonographic appearances until they completely resolve.[8] Although the concept of a physiologic cyst in a postmenopausal woman is rare, ovarian follicles at various stages of maturity can arise in the amenorrheic perimenopausal woman.

Endometriosis is a relatively common gynecologic entity in women of reproductive age and occurs in 10–15% of menstruating women. It is characterized by proliferation of glandular and stromal endometrial cells outside the uterus; the inflammation and anatomic distortion associated with this condition can give rise to problems of dysmenorrhea, dyspareunia, and infertility. Whereas endometriosis may manifest in many forms, the most common sonographically detected lesion is the ovarian endometrioma, or chocolate cyst. Like the hemorrhagic functional cyst, the sonographic appearance of the ovarian endometriomas can vary, often demonstrating internal echoes resulting from the breakdown of blood products.

Hydrosalpinx is a cystic dilation of the fallopian tube that may occur either as a consequence of a pathologic process that leads to distal tubal occlusion (eg, previous pelvic inflammatory disease, endometriosis, fallopian tube carcinoma, or tubal pregnancy). There also may be no obvious precipitating factors. Sonographic features in the absence of malignancy include a tubular shape that often also demonstrates incomplete septations or short linear projections.

Within each type of neoplasm, tumors can be benign or malignant based on their inherent capacity to invade and metastasize and are further broadly classified according to the cell type from which they originate.[2,6,7] Epithelial tumors also contain a subclass of "borderline" or "low-malignant-potential" tumors

Table 1. Characteristics of Commonly Encountered Ovarian Neoplasms

	Mean or Median Age at Presentation (y)	% of All Ovarian Neoplasms	Relative Frequency (%)	% Stage I at Presentation	Approximate 5-Year Survival (%)
Epithelial		60			
Benign	45		50–80		
Borderline	48		15–20	90	−95
Malignant	63		5–30		
Type I (low-grade)	43		10	−90	−75
Type II (high-grade)	60		90	−25	−30
Germ cell		28			
Mature cystic teratoma	30		98		
Malignant germ cell	16–20		2	60–70	−90
Sex cord stromal		10			
Fibroma or theca-fibroma	46		78		
Granulosa cell malignancy	46		12	83–87	−90
Other		2			

Data from references 2, 9, 95, and 96.

that are histologically and biologically unique. Important differences in the clinical characteristics of the ovarian neoplasms exist (Table 1).

Benign neoplasms are the most common ovarian tumors within any histologic subtype, with serous or mucinous cystadenomas arising from the ovarian epithelium, fibromas and fibro-thecomas arising from the ovarian stroma, and mature cystic teratomas arising from the ovarian germ cell. Epithelial tumors are the most common form. They account for 60% of all ovarian neoplasms and up to 90% of primary ovarian cancers. Sex-cord stromal tumors account for 10–15% of all neoplasms; germ cell tumors account for 25% of ovarian neoplasms, the majority of which are benign.[2,6,7]

The biologic behavior of the ovarian malignancies differs substantially. Nonepithelial cancers typically present at an early stage, often with bulk symptoms related to large masses and high associated 5-year survival rates (Table 1). By contrast, the majority of ovarian cancer deaths are attributed to epithelial ovarian carcinoma.[5,6,9] However, studies have shown that epithelial ovarian cancer is not a single disease but is composed of two biologically distinct groups of tumors that can be classified based on their morphologic and molecular features.[10,11] One group of tumors, designated type I, are low-grade and behave in a much more indolent fashion. These tend to remain confined to the ovary for long periods of time despite often achieving large size. They are relatively genetically stable but molecular and histologic analyses suggest an evolution through a stepwise mutational process from borderline epithelial neoplasms. In contrast, type II neoplasms are highly aggressive and include conventional high-grade serous carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors (carcinosarcoma). Unlike type I epithelial ovarian cancer, these lesions appear to arise as de novo events, rather than from precursor lesions, and often disseminate rapidly. They typically present at an advanced stage and it is these tumors that are responsible for the majority of ovarian cancer deaths.[9,10] By necessity, any effective strategy designed to reduce the overall mortality attributable to ovarian cancer must focus on identifying type II epithelial ovarian cancer.

RISK FACTORS FOR OVARIAN CANCER

Age

Age is the most important independent risk factor for epithelial ovarian cancer. Epithelial ovarian cancer is infrequent in women younger than 40 years of age. Incidence and mortality increase sharply after menopause; the average age at diagnosis is 60 years, and a peak rate of 57 per 100,000 women is seen in their early 70s[12,13] (Table 2). In general, type I epithelial ovarian cancer occurs much more commonly in younger women than type II epithelial ovarian cancer.[6,7,12,13] For example, sex cord stromal tumors and germ cell tumors are found more commonly in younger women who are premenopausal.[2,6,7] Although ovarian

Table 2. Risk of Ovarian Cancer Stratified by Age

Age (y)	Risk
40	1 in 2,500
50	1 in 1,500
60	1 in 600
70	1 in 400

Data from reference 12.

cancer is relatively rare in young women, when it does occur it is more likely to be a more indolent type I epithelial or a nonepithelial subtype (Table 1).

Family History

Up to 10% of women with ovarian cancer have inherited a germline mutation in a tumor suppressor gene that places them at increased risk for the disease.[14] Of the inherited ovarian cancers, more than 90% result from *BRCA1* or *BRCA2* germline mutations, and the remaining 10% result from mutations that are associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome) or are unexplained. These mutations increase a woman's lifetime risk ovarian cancer up to approximately 40–45% (*BRCA1*) and 10–20% (*BRCA2* and *HNPCC*).[15–17] Even among women harboring *BRCA1* and *BRCA2* genetic mutations, risk for malignancy is still highly dependent on age, with ovarian cancer rates less than 1% in carriers younger than 40 years old (Table 3).

In the absence of formal genetic testing, family history can still allow insight into risk. Compared with the lifetime risk of 1.6% for the general population, a woman with a single first-degree family member affected by ovarian cancer has a 4–5% lifetime risk.[18] In cases in which there are two first-degree relatives, a woman's risk increases to 7%, with a nonnegligible subset of these families demonstrating evidence for an identifiable predisposing genotype such as a *BRCA1* or *BRCA2* mutation.

Most hereditary ovarian cancers arise from mutations in either the genes *BRCA1* and *BRCA2* or the mismatch repair genes as in hereditary nonpolyposis colorectal cancer syndrome, both of which are inherited in an autosomal-dominant fashion and are thought to function as tumor suppressor genes. Because patients with a hereditary genetic predisposition have additional characteristics in their personal and family history that can identify them as potential carriers, the American College of Obstetricians and Gynecologists (the College) has suggested referral for formal genetic risk assessment in sufficiently at-risk individuals.[19] Features suggestive of such mutations in an individual family include:

- Multiple relatives with breast cancer, ovarian cancer or both (as in *BRCA1/2*) or colon and other gastrointestinal, endometrial, or pancreatic malignancies (as in hereditary nonpolyposis colorectal cancer syndrome), often with a predominance of early-onset cases.
- Women with more than one primary cancer, such as bilateral breast cancer or breast plus ovarian cancer.
- Cancer being diagnosed in a family member younger than age 50.
- Evidence of vertical transmission in two or more generations (consistent with autosomal-dominant inheritance).

Clinicians must also consider the many potential limitations in ascertaining genetic risk when obtaining a family history, which include:

- A patient's limited knowledge about her family clinical history.
- Families that are not highly informative because of small or few female members.
- The variable penetrance of the phenotype within individual families harboring deleterious mutations.

Table 3. Risk of Ovarian Cancer in *BRCA1* and *BRCA2* Carriers Stratified by Age

Age (y)	*BRCA1* (%)	*BRCA2* (%)
20	Approximately 0	Approximately 0
30	Less than 1	Approximately 0
40	0.87–1.49	Less than 1
50	0.96–1.19	0.60–0.75
60	2.26–2.49	0.38–0.42

Data from reference 97.

Symptoms

Several case–control studies have found that women with ovarian cancer commonly experience a pattern of symptoms that include bloating, pelvic or abdominal pain, difficulty eating or early satiety, urinary urgency or frequency, or constipation.[20–24] These symptoms are more commonly associated with ovarian cancer when they are newly experienced and also if they occur more than 12 times per month.[21] A scoring system based on these data, termed the ovarian cancer symptom index, has been promoted as a potentially useful screening tool,[18] albeit with positive predictive values of less than 2%.[25] Whereas symptom assessment may not be an efficient screening tool for the general population, persistent symptoms such as those described in a woman identified to have an adnexal mass should raise one's index of suspicion for malignancy.

Other Epidemiologic Associations

Additional risk factors associated with an increased risk for ovarian cancer include reproductive and hormonal factors such as nulliparity, early menarche, and late menopause.[26–28] Although infertility is identified with associated increased risk, recent evidence

suggests that fertility drug use is not an independent risk factor for ovarian cancer.[29,30]

UNDERSTANDING THE DIAGNOSTIC STUDIES

The likelihood of a malignancy varies among women with an adnexal mass based on a number of clinical, genetic, and epidemiologic risk factors. This pretest probability, in turn, affects the positive and negative predictive value of any given diagnostic test.[31,32] As such, the selection and interpretation of diagnostic tests obtained must be considered in the context of each individual's pretest probability for harboring malignancy. Appropriate clinical decision-making is further enhanced by an understanding of the inherent accuracy of each diagnostic test considered. Unfortunately, published studies of the accuracy of available diagnostic tests with respect to ovarian cancer report widely varying results and interpretation of the literature in this regard can be complex. A large proportion of the reported differences in test performance relate to differences in the prevalence of ovarian cancer in the populations included in these investigations. For example, positive predictive values that are reported from screening studies in the general population of women will differ substantially from those seen in a population of select postmenopausal women with known adnexal masses who are awaiting surgery. For the purposes of this review, care is taken to distinguish between reports generated from screening studies, which are presented for illustrative purposes, from studies that focus on women with known adnexal masses.

Pelvic Examination

As a screening tool, the traditional pelvic examination performs poorly.[33] An adnexal mass that is identified in an asymptomatic woman during annual screening pelvic examination has a far greater probability of representing a benign process than a malignant one, with a reported positive predictive value of only 0.4%.[2] The low positive predictive value is mainly attributable to the low prevalence of ovarian cancer in the general population; moreover, the predominance of benign disease identified through annual screening pelvic examination underscores the observation that screening programs are biased to detect prevalent lesions with indolent biology.[34,35]

Pelvic examination features such as nodularity or irregular contour, solid consistency, and fixed position suggest malignancy; however, studies evaluating the ability to distinguish benign from malignant disease by pelvic examination features from women with known adnexal masses awaiting surgery also report disappointing results.[36,37] Slightly higher positive predictive values are seen in the postmenopausal population of women[2,33] and in women with relevant symptoms, as delineated by the ovarian cancer symptom index.[21]

Imaging Studies: Ultrasonography, Two-Dimensional, Three-Dimensional, Doppler, and Scoring Systems

Conventional gray-scale transvaginal ultrasonography is the most common imaging modality used to evaluate adnexal structures. High-frequency transvaginal probes allow a detailed morphologic view of the adnexal structures, whereas color Doppler techniques allow analysis of vascular flow characteristics within the mass. Ultrasonography generally is considered a highly sensitive test for identifying an adnexal mass, with a somewhat reduced specificity with respect to distinguishing benign from malignant (Table 4).

When using ultrasonography in their own practice, clinicians also should consider that image quality and accuracy of pelvic ultrasonography are both equipment- and operator-dependent.[39,40] Prospective trials that report on the accuracy of ultrasonography in discriminating benign from malignant adnexal masses are typically undertaken under optimal conditions using contemporary high-resolution equipment with a limited number of experts performing and interpreting the scans. As such, the accuracy reported in these studies may be higher than that seen outside of this controlled environment.

To overcome some of the subjective elements of interpretation and improve reproducibility, a variety of morphologic scoring systems have been developed and evaluated either alone or in combination with

Table 4. Sensitivity and Specificity of Various Diagnostic Screening Approaches for Adnexal Mass

Ultrasound Scoring System	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Sassone (1991)	0.86 (0.79–0.91)	0.77 (0.73–0.81)
Ultrasound: Doppler resistance index	0.72 (0.61–0.82)	0.90 (0.84–0.94)
Ultrasound: morphology plus Doppler	0.86 (0.79–0.91)	0.91 (0.80–0.97)
Pelvic MRI: 15 studies	0.91 (0.86–0.94)	0.87 (0.83–0.90)
CA 125 (threshold more than 35)	0.78 (0.75–0.81)	0.78 (0.71–0.82)

CI, confidence interval; MRI, magnetic resonance imaging.
Modified from reference 2.

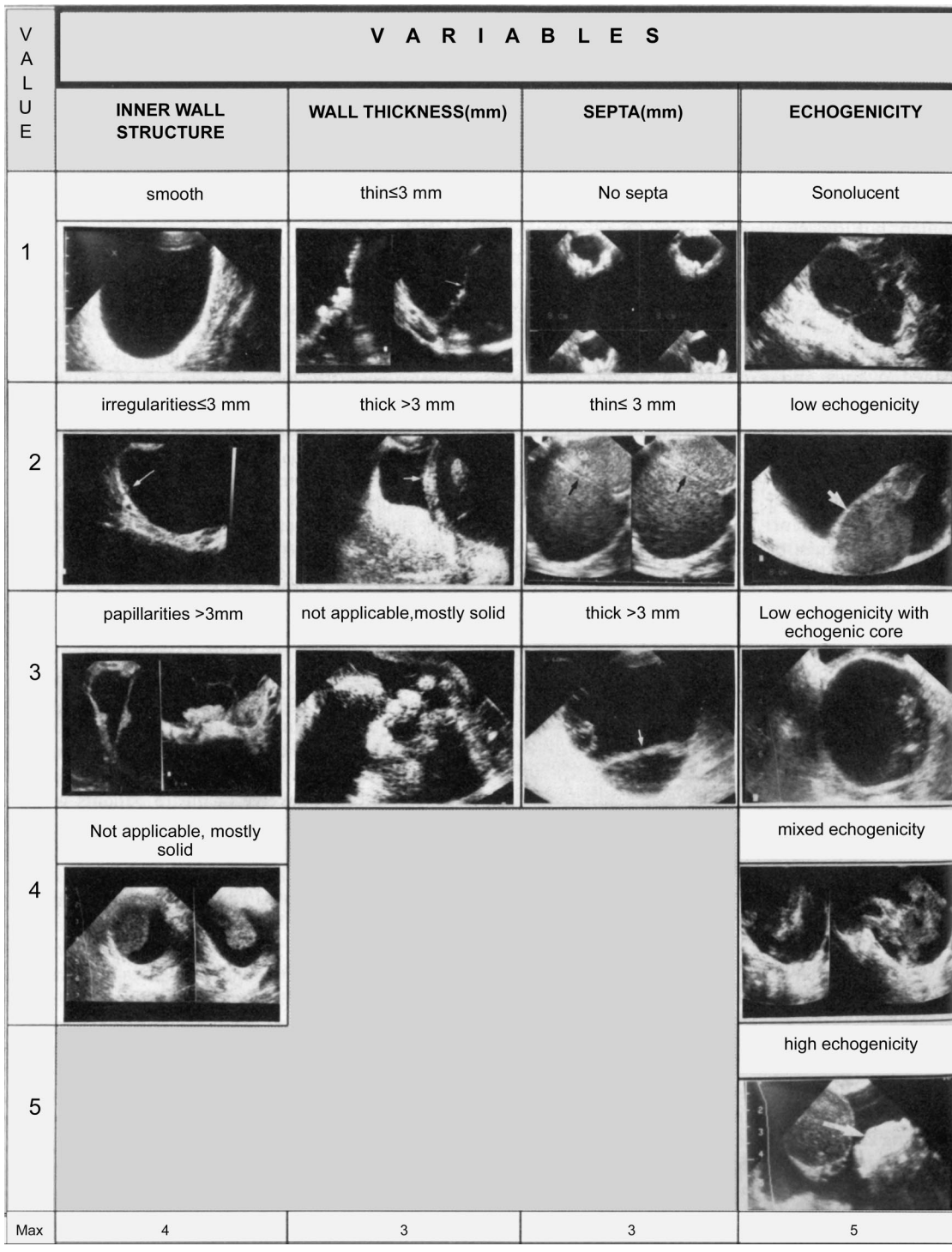

Fig. 1. Scoring system for evaluation of abnormal ovaries. Reprinted from Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. Obstet Gynecol 1991;78:70–6.

Liu. Management of the Adnexal Mass. Obstet Gynecol 2011.

color flow Doppler or select patient characteristics or both.[41–46] Sonographic findings are documented and weighted according to the strength of their association with malignancy. Relevant anatomic details of the most extensively characterized scoring systems typically includes: wall structure ranging from smooth to papillary projections of variable size; presence of septa ranging from thin to thick; and echogenicity ranging from sonolucent to highly echogenic. Cut-off values are assigned that categorize masses as either malignant or benign and, in general, thresholds that favor sensitivity will compromise specificity.[31] Select scoring systems have been validated by prospective studies. The most extensively evaluated is the Sassone scoring system (Fig. 1). A comprehensive meta-analysis prepared for the Agency for Healthcare Research and Quality indicates a pooled sensitivity of 86% and specificity of 77% in distinguishing the benign from malignant adnexal mass using that scoring system.[2] Despite different designs, several purely sonographic scoring systems performed fairly similarly when simultaneously applied to the same study population.[2,47] In general, positive predictive values are lower and negative predictive values are higher when scoring criteria are applied to premenopausal populations.[2]

Three-dimensional ultrasonography has been less extensively studied, but initial reports suggest possible improved performance compared with two-dimensional ultrasonography.[48–52] The sensitivity of three-dimensional ultrasonography for identifying malignancy among women with an adnexal mass ranged from 78–100%. Reported specificities that range from 78–92% and negative predictive values of 95–99% are generally improved as compared with those of two-dimensional ultrasonography. These findings suggest that three-dimensional sonography is more accurate and may be appropriate in the further triage of the intermediate-risk adnexal mass identified by two-dimensional imaging.

Inherent limitations in the specificity of ultrasonography imaging relate to the overlap in the morphologic characteristics of benign, borderline, and malignant masses.[53] Color Doppler ultrasound imaging adds another dimension of information by providing an assessment of tumor vascularity. Malignant neoplasms recruit blood vessels through angiogenesis that are lower-resistance and higher-flow than vasculature associated with normal ovaries or benign neoplasms. The resistance index, the pulsatility index, and the maximum systolic velocity are parameters that objectively quantify vessel flow characteristics to distinguish high- and low-resistance vessels. The addition of Doppler interrogation of adnexal masses

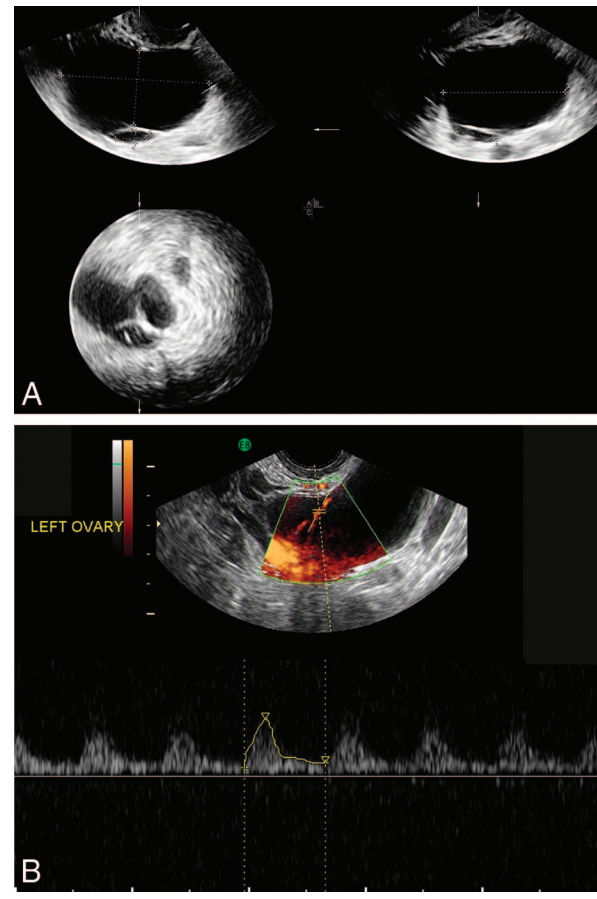

Fig. 2. A. Two-dimensional and three-dimensional ultrasound images of a 73-year-old menopausal woman presenting with a 6-cm left ovarian cystic mass with septation. **B.** Doppler interrogation of the septal wall of the cyst demonstrated blood flow within the septum suggestive of malignancy. Histopathology of the lesion was serous cystadenoma. Images courtesy of Noam Lazebnik, MD.
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appears to offer improved specificity over two-dimensional ultrasonography[2] (Table 4). However, as with two-dimensional ultrasonography, a spectrum of vascular patterns exists and there are inherent overlaps in flow characteristics that are also reported in benign, borderline, and malignant neoplasms.[46] Figures 2A and 2B illustrate the application of two-dimensional and three-dimensional ultrasound technology with Doppler flow studies for evaluation of a 73-year-old menopausal women presenting with a large left adnexal cystic mass. Doppler interrogation demonstrated blood vessels and blood flow in the septa, suggestive of malignancy. Surgical exploration and excision revealed a serous cystadenoma.

Although ultrasound scoring systems and Doppler studies have the potential to improve diagnostic

accuracy and reduce the subjective elements of interpretation, in clinical practice they are not used consistently among radiologists and often they are not used at all. At present, most ultrasound reporting of adnexal masses is purely descriptive. Moreover, descriptive language in ultrasound reporting is not standardized. Clinicians who rely solely on descriptive ultrasound reporting, however, may allow bias in their decision-making based purely on nuance of language. For this reason, it is the authors' opinion that clinicians should consider adopting the practice of additionally personally reviewing ultrasound images in question as they make their clinical correlations.

Additional Imaging Modalities

Because of much higher cost, other imaging modalities such as contrast-enhanced magnetic resonance imaging (MRI), computed tomography, and positron emission tomography are not recommended for the initial evaluation of adnexal masses. However, these modalities may play a role for selected indications. Magnetic resonance imaging distinguishes subtle differences in tissue signals and provides enhanced anatomic detail over traditional gray-scale pelvic ultrasonography, and also offers the ability to characterize nonadnexal pelvic pathology. Studies evaluating its performance in the discrimination of adnexal masses are numerous and suggest somewhat improved specificity over ultrasonography, with a pooled specificity reported at 87%.[2] Thus, MRI also may play a role in the additional investigation of the intermediate risk adnexal masses identified by two-dimensional ultrasonography.

Although computed tomography imaging allows some morphologic detail of adnexal masses, its most common application is in the evaluation of a woman with a known adnexal mass in which additional imaging of abdominal and pelvic organs are needed. These cases occur most commonly when cancer or nonadnexal pathology is suspected.

Serum Biomarkers: CA 125

The most extensively investigated serum marker for ovarian cancer is the CA 125. Tissues derived from coelomic epithelium produce the antigen CA 125, and serum levels of this antigen are elevated in 80% of women with epithelial ovarian cancer.[54] The CA 125 antigen is also expressed by various other pathologic and normal tissues of mullerian origin, and thus serum values can be elevated in a number of unrelated gynecologic and nongynecologic conditions such as endometriosis, pregnancy, and pelvic inflammatory disease. As such, it has a low specificity, especially in premenopausal women. In premenopausal women with a pelvic mass, the positive predictive value at cut-off thresholds more than 65 units/mL was 49%, with specificity and positive predictive values significantly higher at higher CA 125 cut-offs and in the postmenopausal population.[55] The sensitivity of the CA 125 is also limited in that it is elevated in only 50% of stage I epithelial ovarian cancer and it is not as commonly elevated in nonepithelial ovarian cancers, such as germ cell and stromal tumors as well as nonserous epithelial subtypes.[2,55] Studies have demonstrated that sensitivity for detecting malignancy in the screening setting is improved when analyzing interval change using serial CA 125 measurements with reference to an individual's baseline CA 125 level.[56–58]

Other Biomarkers Combinations and Proteomics

A variety of serum proteins have been identified that have been considered for their potential for detecting ovarian carcinoma, either alone or in combination with CA 125. Proteomic technology also has been investigated to determine if serum protein profiling patterns could be used to distinguish between cancer and benign masses.

OVA1

In September 2009, the Food and Drug Administration approved a serum-based test called OVA1 (multivariate index assay) "as an adjunct to clinical decision-making for women 18 years and older who are planning surgery for an adnexal mass."[59] The test combines the five separate serum protein marker results as well as menopausal status into a single numerical score between 0 and 10 to indicate the likelihood that the pelvic mass is benign or malignant. For approval, the Food and Drug Administration reviewed a study of 516 patients, including 269 evaluated by nongynecologic oncologists, which compared multivariate index assay results with surgical results.[60] When combined with presurgical information, such as radiography and other laboratory tests, results from the multivariate index assay test identified additional patients who might benefit from oncology referral who were not identified using presurgical information alone. It is important to emphasize that it is not approved for ovarian cancer screening and is not intended to replace clinical judgment as a stand-alone test. Confirmatory studies are underway. The cost of the multivariate index assay test is approximately $650 and also must be considered when deciding among diagnostic tests. Other serum bio-

markers, such as β-human chorionic gonadotropin (hCG), lactate dehydrogenase, and α-fetoprotein may be elevated with select germ cell neoplasms, whereas inhibin A and B may be elevated in granulosa cell tumor of the ovary.

GENERAL DIAGNOSTIC CONSIDERATIONS

An accurate pretest probability is essential to subsequent management. Consequences of an inaccurate pretest probability include subsequent poor test selection, poor interpretation of results, and, ultimately, diagnostic and management error. The probability of harboring malignancy is refined using available clinical, genetic, and epidemiologic risk factors, in conjunction with index diagnostic testing. Cases of very low clinical risk identified to harbor an adnexal mass of moderate complexity on imaging studies may not require further testing. However, cases of intermediate clinical risk with the same imaging study findings may be triaged to further testing to optimize diagnostic sensitivity or possibly even surgery. The following discusses additional diagnostic considerations in the patients at low, intermediate, and high risk who are identified to harbor an adnexal mass.

Low-Risk Adnexal Masses

If both pretest probability assessment and imaging studies demonstrate an adnexal mass with a low probability of malignancy, then additional tests with low specificity are to be avoided. Such tests are associated with a high rate of false-positive results without appreciable improvements in sensitivity; moreover, false-positive test results often compel clinicians to pursue confirmatory studies that are expensive as well as stressful to the patient. Therefore, whereas inexpensive and noninvasive, the injudicious use of low-specificity tests such as CA 125 in a low-risk setting (ie, premenopausal women) may ultimately be costly without adding clarity.

Intermediate-Risk Adnexal Masses

Perhaps the most challenging from a decision-making standpoint are cases of intermediate risk for malignancy. The entities on the differential diagnosis for the intermediate risk mass are broader. Whereas most indeterminate masses still result from common benign conditions, a subset will represent cancer. For optimal clinical decision-making in this setting, it is particularly essential to have an accurate understanding of the pretest probability and the inherent accuracy of the diagnostic test.

A large proportion of intermediate-risk adnexal masses represent benign entities. Tests with greater specificity allow point-of-care triage that may obviate the need for surgery that would otherwise be purely for diagnostic purposes; in the case of malignancy, however, they would potentially offer a more timely diagnosis than a "wait and watch" strategy of interval ultrasound re-examination. In select individuals, three-dimensional ultrasonography or MRI, with reported improved specificity and negative predictive value as compared with two-dimensional ultrasonography, may be potentially useful to further triage the intermediate-risk adnexal mass. Additionally, tumor markers such as CA 125 may be selectively obtained, particularly in the postmenopausal population in which specificity is higher. Alternatively, surgical evaluation can be considered if the perceived risk for malignancy justifies this intervention.

High-Risk Adnexal Masses

In high-risk settings in which active intervention is likely if an anticipated condition is confirmed, diagnostic studies that favor high negative predictive values are preferred. If, however, there is sufficiently high risk, then additional diagnostic studies may not be necessary and clinicians may wish to proceed with studies most relevant to surgical planning or gynecologic oncology referral.

THERAPEUTIC APPROACH

When considering management, it is again useful to consider low-risk, intermediate-risk, and high-risk categories based on clinical assessment and diagnostic studies. Although accepted definitions for low, intermediate, and high probability for malignancy do not presently exist, clinicians must carefully weigh perceived risks and benefits when they consider appropriate thresholds for surgical intervention in any given individual. It is emphasized that thresholds for surgical intervention are relative and the risk of a delayed diagnosis must be weighed against the risks as well as personal and financial costs of over-testing and over-intervention in any given individual.

LOW-RISK ADNEXAL MASS (NO SURGICAL INTERVENTION)

Asymptomatic adnexal masses that have a low probability of representing a malignancy (less than 1%) may be managed without intervention. In women with suspected benign masses in whom nonoperative management is elected, interval follow-up testing is typically recommended. In general, the purpose of a follow-up protocol is to capture prevalent disease that was missed by imperfectly sensitive diagnostic tests, to identify benign lesions that progress into something

biologically significant (ie, transition into cancer), and to help avoid over-treatment of biologically insignificant lesions (ie, asymptomatic, benign, or inactive ovarian cysts). There are limited comparative data specifically evaluating either timing or method of follow-up in women with adnexal masses who are managed without active surgical intervention. In the absence of evidence when deciding among follow-up options, the purpose of a follow-up protocol must be analyzed in the context of the entities on the differential diagnosis and the anticipated outcomes.

Simple ovarian cysts have a low risk (less than 1%) for harboring malignancy.[2,61–65] Whether simple ovarian cysts represent benign neoplasms, inclusion cysts, or functional cysts, the biologic potential and natural history of the simple ovarian cyst have been characterized through morphologic, molecular epidemiologic, and prospective observational screening studies. Central to a debate on the nonsurgical management of the unilocular ovarian cyst is the question whether epithelial ovarian cancer arises as a de novo event or represents a transition from a pre-existing benign epithelial cyst. If benign epithelial ovarian neoplasms were thought to represent precursor lesions or in any way indicate increased risk for malignancy, then the threshold for surgical intervention for a given simple cystic adnexal mass would be greatly influenced by this association.

Numerous studies have carefully analyzed the histologic and genetic features of established epithelial ovarian neoplasms and normal ovaries removed from women at high risk with a history of hereditary ovarian cancer to determine whether common features such as serosal inclusions, epithelial pseudostratification, and metaplasias represent precursor lesions.[10,66–68] Whereas borderline epithelial cancer likely represents a precursor to type I epithelial carcinoma, such studies have not convincingly identified that benign epithelial ovarian cysts increase risk for ovarian malignancy.[9,10,66–68]

Further lending support to this theory are cohort and large prospective observational studies that indicate the removal of persistent simple ovarian cysts is not associated with a decrease in the proportion of expected deaths from ovarian cancer relative to other cancers,[69] and that monitoring of patients with unilocular ovarian cysts smaller than 10 cm without intervention is not associated with evidence of malignant transformation over the course of prolonged observation.[61–65]

Thus, the present literature indicates that it may not always be necessary to surgically remove asymptomatic unilocular ovarian cysts thought to represent benign entities. Further, it implies that the purpose of a follow-up protocol in this setting is to capture prevalent ovarian cancer that may have been missed by imperfectly sensitive index diagnostic imaging studies, rather than that of monitoring for benign processes that may transform into malignant. Although studies may vary in length of follow-up, method of follow-up, and threshold for intervention, most studies reporting follow-up in women with unilocular ovarian cysts use interval ultrasonography at 3- to 6-month intervals, often in conjunction with repeat CA 125 testing.[61–65] Protocols using repetitive ultrasound examinations at intervals of 3- to 6-month examinations appear quite safe[2] and cancers identified during follow-up are rare (less than 1%).

Although it is implicit that interval imaging ultrasound studies may be discontinued after documented resolution of an ovarian cyst, there are no established guidelines for when to discontinue imaging evaluations in unilocular ovarian cysts that have proven stable with respect to size and morphologic characteristics during repeat interval evaluations. However, if the purpose of this follow-up is to capture prevalent disease (ovarian cancer) that was missed by an imperfectly sensitive index test rather than monitoring for possible progression of a benign lesion to that of a malignant neoplasm, then a limited series of repeat diagnostic tests should sufficiently increase the diagnostic sensitivity of that test to safely exclude a malignancy with acceptable reliability.[70] Although there are no established guidelines in this regard, it is the authors' opinion based on these data that one or two ultrasound examinations at 3- or 6-month intervals, provide sufficient diagnostic sensitivity for follow-up of a simple unilocular ovarian cyst that are stable or decreasing in size. Limited serial CA 125 also may be considered if clinical indicators otherwise suggest potential increased risk. Patients triaged to this strategy may harbor fear and misconceptions, and it is imperative that the clinician provide consistent and clear information, perhaps reinforced by informational written material, to reassure them regarding the biology of their ovarian cyst and the safety of the clinical plan. In the authors' opinion, effective patient education regarding the low-risk adnexal mass virtually can eliminate surgery performed solely to relieve patient or family anxiety.

In the case of significant morphologic change during follow-up, surgical intervention may be warranted. Unfortunately, thresholds to define significant morphologic change have not been defined. When establishing expectations for and interpretation of interval follow-up studies, it is instructive to consider the natural history of unilocular ovarian cysts as

defined by longitudinal ultrasound studies in both the premenopausal and postmenopausal populations.

Premenopausal Population

Adnexal masses thought to represent functional or physiologic cysts in premenopausal women involute in a variable period of time, typically resolving in less than 3 months.[71] Whereas oral contraceptives do not hasten the resolution of functional cysts,[72] they may play a role in reducing possible symptoms of pain and menstrual irregularities as well as in enhancing the interpretability of follow-up imaging studies through ongoing ovulation suppression.[73]

Postmenopausal Population

Among a cohort of 15,735 women undergoing 4 years of transvaginal ultrasound screening from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 54% of identified cysts remained unchanged and 34% resolved spontaneously at 1 year.[65] Although 12% of women had morphologic change develop, there were no invasive ovarian cancers identified that were attributable to the identified index unilocular cyst. Moreover, an 8–12% annual incidence of new simple cysts was documented among postmenopausal women, and this is consistent with other published data.[74] Taken together, these data suggest that a protracted follow-up protocol that uses multiple interval imaging studies may increase the probability of invasive intervention without necessarily improving diagnostic ability as it relates to the end point of interest: detection of ovarian cancer.

INTERMEDIATE RISKS ADNEXAL MASS (POSSIBLE SURGICAL INTERVENTION)

For women with intermediate-risk adnexal masses based on careful consideration of baseline risk and results of diagnostic testing, greater scrutiny of the trade-off in risk for intervention compared with nonintervention is necessary. There is a nonnegligible risk for malignancy (more than 1%) that can be stratified based on careful consideration of baseline clinical risk factors and results of diagnostic testing. The majority of adnexal masses of intermediate sonographic complexity are benign and often represent endometriomas, hemorrhagic cysts, hydrosalpinges, and benign neoplasms. However, a small proportion will represent malignancy. The potential for malignancy and consequences of a delay in intervention for significant pathology as well as the cost and potential morbidity associated with surgery, if performed only for diagnostic purposes, need to be considered.

When managing the intermediate-risk adnexal mass, the fear of a delay in the diagnosis of an ovarian cancer strongly influences clinical decision-making. Therefore, it is appropriate to understand the potential consequences of a delay in diagnosis. Cure rates for ovarian cancer are significantly higher when detected in early stages; as such, a delay in diagnosis of a potentially stage I ovarian cancer is never desirable, particularly in the case of epithelial ovarian cancer. However, stage I epithelial ovarian cancer is difficult to capture, as illustrated by a recent screening trial of more than 34,000 women in whom 79% of invasive epithelial ovarian cancers detected during annual screening efforts had already metastasized.[35] By contrast, the majority of borderline ovarian carcinomas identified in this study were early stage, thus emphasizing the differences in the biology of these two entities and again underscoring the observation that screening programs are biased to identify masses with indolent biology that are relatively stable. Further lending insight into the difficulty in detecting ovary-confined type II invasive epithelial ovarian cancer are modeling studies that have attempted to estimate the preclinical natural history of serous ovarian carcinoma. Type II epithelial ovarian carcinoma appears to arise as a de novo event, rather than through malignant transformation of a benign precursor lesion; moreover, it is estimated that 90% of the duration of ovary-confined disease (and therefore of the opportunity for early detection) occurs at a lesion diameter of less than 0.9 cm.[5] If already metastatisized, it is assumed that diagnosis of epithelial ovarian cancer at an earlier time point and at a lower burden of tumor will improve the success of treatment; however, the magnitude of survival effect with earlier detection of advanced disease is not yet fully defined.[35]

For women with benign masses, there are also theoretical benefits to surgical excision in the absence of symptoms that may include preventing acute events that may necessitate emergent adnexal surgery. One such condition is ovarian torsion (commonly associated with benign neoplasms, such as cystadenoma or teratoma). Another may be spontaneous cyst rupture (as with mature cystic teratoma, endometrioma). The potential consequences of torsion and cyst rupture, such as hemorrhage and peritonitis, are well-described. In the setting of mature cystic teratoma, intraperitoneal leakage of sebaceous material may result in a dramatic chemical peritonitis.[75,76] Although it is clear that these events are rare among the population of women harboring a benign adnexal mass, the true risk for torsion and spontaneous rupture attributable to an adnexal mass is unknown because the true population prevalence of adnexal masses is unknown. However, in the case of

ovarian dermoid, the reported 15–28% rate of iatrogenic intraoperative rupture and potential associated peritonitis reported in the literature arguably far exceeds the risk for spontaneous rupture.[76]

Whereas benign epithelial neoplasms do not appear to increase risk for epithelial ovarian carcinoma, mature cystic teratoma and endometriosis are benign entities that are associated with an increased risk for subsequent malignancy. Malignancy is reported in 0.17–1% of patients undergoing surgery for these conditions[77–79]; however, the true risk for malignant transformation among the population of women with these conditions is again unknown, as is the overall impact of surgical excision for preventive purposes in this setting.

Surgical Morbidity and Mortality

Central to any decision-making regarding thresholds for adnexal surgery performed for these purposes is an understanding of both the morbidity and mortality risks from surgery. Risks for surgical morbidity and mortality are influenced by a number of variables including: patient characteristics of age and comorbidities; mode of surgery (laparoscopy compared with laparotomy); extent of surgical procedures performed; and diagnosis (cancer compared with benign pathology). Overall mortality risk identified through the Nationwide Inpatient Sample discharge data for laparoscopic management of adnexal masses is low, ranging from 0.2% to 2.3%, whereas rates with mortality risk are higher for laparotomy, ranging from 0.6% to 14%.[2] Whereas rates for mortality identified appear low, operative complications, such as hemorrhage, organ injury, and conversion to laparotomy, occurring are reported in 1.7–22% of women undergoing laparoscopy for an adnexal mass.[2]

Extent of the Surgery

If surgery is undertaken, then the approach and extent of the procedure must also be considered carefully to minimize morbidity risk.

Laparoscopy compared with laparotomy

Laparotomy is typically performed for adnexal masses that are highly suspicious for cancer to facilitate intact removal as well as anticipated surgical staging procedures. Laparoscopy, however, is associated with decreased surgical pain, shorter recovery time, and lower overall costs[80] and is appropriate for low-risk adnexal masses. For the intermediate-risk adnexal mass, the decision regarding surgical approach also may be influenced by technical factors that could hinder intact specimen removal, such as size or anticipated adhesions.

Cystectomy compared with oophorectomy

The choice between ovarian cystectomy and oophorectomy is typically a function of a number of factors, including preoperative diagnosis, patient age, desire for future fertility, and presence of symptoms. For low-risk lesions thought to be consistent with benign cystadenoma, mature teratoma, or endometrioma, ovarian preservation through cystectomy is reasonable, particularly in the premenopausal woman. For intermediate-risk adnexal masses in which a diagnosis of malignancy remains to be excluded, however, one must carefully weigh the risk of cyst rupture and the subsequent potential upstaging of the tumor with the potential benefit of preserving the involved ovary. In postreproductive and postmenopausal women with an intermediate-risk adnexal mass, unilateral salpingoophorectomy with frozen section is a reasonable initial approach. Subsequent surgical intervention is then influenced by the frozen section diagnosis.

The normal contralateral ovary

In the premenopausal woman for whom removal of a normal contralateral ovary has minimal risk-reducing or oncologic benefit, there are several clinical arguments in which preservation of the contralateral ovary is desirable. In addition to the known quality-of-life implications of surgical menopause,[81] overall subsequent mortality risk is increased by early surgical castration attributable to associated increases in cardiovascular mortality and hip fracture.[82] Thus, preservation of the contralateral ovary is desirable in the case of benign unilateral masses or benign bilateral processes amenable to cystectomy. Moreover, there does not appear to be appreciable oncologic benefit to removing a normal contralateral ovary in premenopausal women with select unilateral stage I germ cell, stromal, or borderline epithelial malignancies.[83–85]

Frozen Section Accuracy

Operative decision-making is often dependent on intraoperative pathology consultation. Often decisions regarding additional surgical interventions, such as removal of the contralateral ovary, hysterectomy, or the necessity for staging, will be based on results from frozen-section analysis. The diagnostic accuracy of frozen section has been extensively studied. In a meta-analysis of 14 studies reporting on 3,659 women, acceptable sensitivities and nearly perfect specificities for benign lesions were documented.[86] Distinguishing benign from borderline ovarian tumor was accurate 95%

of the time with the final diagnosis of benign, and frozen-section accuracy increased to 98% in distinguishing malignant tumor from benign. Diagnostic accuracy, however, was substantially less in distinguishing borderline from malignant tumors, with frozen section and final diagnosis in agreement in only 51% of cases. These analyses and others also identify a higher degree of inaccuracy with mucinous tumors as well as large masses.[87,88] These reported uncertainties should be considered when operative decisions are based on these results. Personal dialogue with the pathologist at the time of consultation is recommended because it provides a much more detailed exchange of information that can be helpful to both parties involved.

HIGH-RISK LESION (SURGICAL INTERVENTION AND REFERRAL)

Adnexal masses that are suspicious for cancer based on clinical assessment, transvaginal ultrasonography, and serum tumor markers warrant surgical exploration. Studies have demonstrated that survival is higher in patients with ovarian cancer whose initial treatment was managed by gynecologic oncologists rather than other providers.[89–91] Additionally, second operations for inadequate initial surgical staging or cytoreduction have substantial additive morbidity and cost.

To facilitate proper patient triage, the the College and the Society of Gynecologic Oncologists have published guidelines jointly for the referral of women with pelvic masses that may represent ovarian cancer. The published guidelines for consultation or referral of women who have a pelvic mass that is suspicious for a malignant ovarian neoplasm, as suggested by at least one of the following indicators[92,93] in postmenopausal women:

- Elevated CA 125 level
- Ascites
- A nodular or fixed pelvic mass
- Evidence of abdominal or distant metastasis
- A family history of one or more first-degree relatives with ovarian or breast cancer

and in premenopausal women:

- Very elevated CA 125 level (eg, more than 200 units/mL)
- Ascites
- Evidence of abdominal or distant metastasis
- A family history of one or more first-degree relatives with ovarian or breast cancer

In separate validation studies, as expected, the College–Society of Gynecologic Oncologists guidelines performed well in predicting advanced-stage ovarian cancer because of the nature of advanced-stage disease.[94] However, the guidelines do not perform as well in identifying early-stage disease, especially in premenopausal women, and emphasize the need for further risk stratification based on all available clinical indicators.

CONCLUSIONS

We have outlined our conceptual approach in the management of the adnexal mass. Development of an effective strategy for the evaluation of any clinical condition requires good evidence of the prevalence of the condition at the first diagnostic encounter, knowledge of the biology and natural history of the entities on the differential diagnosis, and understanding of the accuracy of the diagnostic tests to be used. The majority of adnexal masses are benign, with only a subset representing malignant processes. Timely and appropriate intervention for malignant processes must be balanced against the risk for over-testing and over-intervention.

Most malignant neoplasms occurring in the premenopausal populations of women are borderline epithelial, germ cell, or stromal cancers, with a large proportion of patients presenting with bulky and often symptomatic early-stage disease. By contrast, the majority of ovarian cancer deaths are caused by type II serous epithelial cancer, which has a substantially more limited preclinical natural history, often disseminating rapidly before clinical detection. Two-dimensional transvaginal ultrasonography is a sensitive and inexpensive diagnostic tool in the initial evaluation of the adnexal mass; however, the somewhat improved specificity and negative predictive values reported for three-dimensional ultrasonography and pelvic MRI have utility in the further triage of the intermediate risk adnexal mass. Tumor markers may be selectively obtained; however, CA 125 testing in low-risk settings and in premenopausal women may reduce specificity in the overall diagnostic evaluation without improving sensitivity.

Substantial evidence exists that simple unilocular cysts may be managed without intervention using a limited series of interval repeat imaging studies to assess for resolution or stability in size and morphologic characteristics. Intermediate-risk adnexal masses are the most problematic diagnostic and management challenges as the entities on the differential diagnosis are broader and risk for malignancy is increased. For appropriate triage and management, careful consideration of clinical risk, accurate interpretation of diagnostic testing, and greater scrutiny of the trade-off in risk for intervention compared with nonintervention is neces-

sary. High-risk adnexal masses warrant surgical exploration; often, referral to a gynecologic oncologist will be appropriate for appropriate surgical staging and possible tumor debulking.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.
2. Myers ER, Bastian LA, Havrilesky LJ, Kulasingam SL, Terplan MS, Cline KE, et al. Management of adnexal mass. Evidence report/technology assessment No. 130. AHRQ Publication No. 06-E004. Rockville (MD): Agency for Healthcare Research and Quality; 2006.
3. Schorge JO, Modesitt SC, Coleman RL, Cohn DE, Kauff ND, Duska LR, et al. SGO White paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol 2010;119:7–17.
4. Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. J Clin Oncol 2004;22:1315–27.
5. Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer; defining the target for early detection. PLoS Med 2009;6:e1000114.
6. DiSaia PJ, Creasman WT. Clinical gynecologic oncology. 7th ed. St. Louis (MO): Mosby; 2007.
7. Hoskins WJ. Principles and practice of gynecologic oncology. 4th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2005:1419.
8. Jain KA. Sonographic spectrum of hemorrhagic ovarian cysts. J Ultrasound Med 2002;21:879–86.
9. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95(Suppl 1):S161–92.
10. Kurman RJ. Shih IeM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol 2008;27:151–60.
11. Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34:433–43.
12. Surveillance epidemiology and end results. SEER incidence statistics: ovarian carcinoma. Available at: http://seer.cancer.gov/statistics. Accessed April 25, 2011.
13. Goodman MT, Howe HL, Tung KH, Hotes J, Miller BA, Coughlin SS, et al. Incidence of ovarian cancer by race and ethnicity in the United States, 1992–1997. Cancer 2003;97:519–23.
14. Ford D, Easton DF. The genetics of breast and ovarian cancer. Br J Cancer. 1995;72:805–12.
15. Chen S, Iversen ES, Friebel T, Finkelstein D, Weber BL Eisen A, et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J Clin Oncol 2006;24:863–71.
16. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94:1358–65.
17. Dunlop MG, Farrington SM, Carothers AD, Wyllie AH, Sharp L, Burn J, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 1997;6:105–10.
18. Schildkraut JM, Thompson WD. Familial ovarian cancer: a population-based case-control study. Am J Epidemiol 1988;128:456–66.
19. Hereditary breast and ovarian cancer syndrome. ACOG Practice Bulletin No. 103. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;113:957–66.
20. Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis. Cancer. 2000;89:2068–75.
21. Goff BA, Mandel LS, Drescher CW, Urban N, Gough S, Schurman KM, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer 2007;109:221–7.
22. Bankhead CR, Kehoe ST, Austoker J. Symptoms associated with diagnosis of ovarian cancer: a systematic review. BJOG 2005;112:857–65.
23. Lurie G, Thompson PJ, McDuffie KE, Carney ME, Goodman MT. Prediagnostic symptoms of ovarian carcinoma: a case-control study. Gynecol Oncol 2009;114:231–6.
24. Lowe KA, Andersen MR, Urban N, Paley P, Dresher, CW, Goff BA. The temporal stability of the symptom index among women at high-risk for ovarian cancer. Gynecol Oncol 2009;114:225–30.
25. Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst 2010;102:222–9.
26. Titus-Ernstoff L, Perez K, Cramer DW, Harlow BL, Baron JA, Greenberg ER. Menstrual and reproductive factors in relation to ovarian cancer risk. Br J Cancer 2001;84:714–21.
27. Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. Am J Epidemiol 2007;166:894–901.
28. Lacey JV Jr, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin A, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health AARP Diet and Health Study Cohort. J Natl Cancer Inst 2006;98:1397–405.
29. Mahdavi A, Pejovic T, Nezhat F. Induction of ovulation and ovarian cancer: a critical review of the literature. Fertil Steril 2006;85:819.
30. Jensen A, Sharif H, Frederiksen K, Kjaer S. Use of fertility drugs and risk of ovarian cancer: Danish population based cohort. BMJ 2009;338:249.
31. Black ER, Bordley DR, Tape TG, Panzer RJ, editors. Diagnostic strategies for common medical problems. 2nd ed. Philadelphia (PA): American College of Physicians; 1999.
32. Richardson WS. Five uneasy pieces about pre-test probability. J Gen Intern Med. 2002;17:891–2.
33. Grover SR, Quinn MA. Is there any value in bimanual pelvic examination as a screening test. Med J Aust 1995;162:408–10.
34. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;15:1685–92.
35. Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009;113:775–82.
36. Padilla LA, Radosevich DM, Milad MP. Limitations of the pelvic examination for the evaluation of the female pelvic organs. Int J Gynecol Obstet 2005;88:84–8.
37. Ong S, Duffy T, Murphy J. Transabdominal ultrasound and its correlation with clinical findings in gynaecology. Ir J Med Sci 1996;165:268–70.
38. Finkler NJ, Benacerraf B, Lavin PT, Wojciechowski C, Knapp RC. Comparison of serum CA 125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. Obstet Gynecol 1988;72:659–64.

39. Yamashita Y, Torashima M, Hatanaka Y, Harada M, Higashida Y, Takahashi M, et al. Adnexal masses: accuracy of characterization with transvaginal US and precontrast and postcontrast MR imaging. Radiology 1995;194:557–65.

40. Timmerman D, Schwärzler P, Collins WP, Claerhout F, Coenen M, Amant F, et al. Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. Ultrasound Obstet Gynecol 1999;13:11–6.

41. Granberg S, Norström A, Wikland M. Tumors in the lower pelvis as imaged by vaginal sonography. Gynecol Oncol 1990;37:224–9.

42. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97:922–9.

43. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. Obstet Gynecol 1991;78:70.

44. DePriest PD, Shenson D, Fried A, Hunter JE, Andrews SJ, Gallion HH, et al. A morphology index based on sonographic findings in ovarian cancer. Gynecol Oncol 1993;51:7–11.

45. Ferrazzi E, Zanetta G, Dordoni D, Berlanda N, Mezzopane R, Lissoni AA, et al. Transvaginal ultrasonographic characterization of ovarian masses: comparison of five scoring systems in a multicenter study. Ultrasound Obstet Gynecol 1997;10:192–7.

46. Alcázar JL, Jurado M. Using a logistic model to predict malignancy of adnexal masses based on menopausal status, ultrasound morphology, and color Doppler findings. Gynecol Oncol 1998;69:146–50.

47. Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BW. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstet Gynecol 2009;113(2 Pt 1):384–94.

48. Kurjak A, Kupesić S. Three dimensional ultrasound and power doppler in assessment of uterine and ovarian angiogenesis: a prospective study. Croat Med J 1999;40:413–20.

49. Kurjak A, Kupesic S, Sparac V, Kosuta D. Three-dimensional ultrasonographic and power Doppler characterization of ovarian lesions. Ultrasound Obstet Gynecol 2000;16:365–71.

50. Geomini PM, Coppus SF, Kluivers KB, Bremer GL, Kruitwagen RF, Mol BW. Is three-dimensional ultrasonography of additional value in the assessment of adnexal masses? Gynecol Oncol. 2007;106:153–9.

51. Alcázar JL, Galán MJ, García-Manero M, Guerriero S. Three-dimensional sonographic morphologic assessment in complex adnexal masses: preliminary experience. J Ultrasound Med 2003;22:249–54.

52. Alcázar JL, Castillo G. Comparison of 2-dimensional and 3-dimensional power-Doppler imaging in complex adnexal masses for the prediction of ovarian cancer. Am J Obstet Gynecol 2005;192:807–12.

53. Valentin L, Ameye L, Jurkovic D, Metzger U, Lécuru F, Van Huffel S, Timmerman D. Which extrauterine pelvic masses are difficult to correctly classify as benign or malignant on the basis of ultrasound findings and is there a way of making a correct diagnosis? Ultrasound Obstet Gynecol 2006;27:438–44.

54. Bast RC Jr, Klug TL, St. John E, Jenison E, Niloff JM, Lazarus H, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med 1983;309:883–7.

55. Malkasian GD Jr, Knapp RC, Lavin PT, Zurawski VR Jr, Podratz KC, Stanhope CR, et al. Preoperative evaluation of serum CA 125 levels in premenopausal and postmenopausal patients with pelvic masses: discrimination of benign from malignant disease. Am J Obstet Gynecol 1988;159:341–6.

56. Skates SJ, Menon U, MacDonald N, Rosenthal AN, Oram DH, Knapp RC, et al. Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmenopausal women. J Clin Oncol 2003;21(10 Suppl):206s–10s.

57. Menon U, Skates SJ, Lewis S, Rosenthal AN, Rufford B, Sibley K, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol 2005;23:7919–26.

58. Lu KH, Skates SJ, Bevers TB, Newland W, Moore RG, Leeds L, et al. A prospective U.S. ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA). J Clin Oncol 2010;28(Suppl):5003.

59. U.S. Food and Drug Administration. FDA news release: FDA clears a test for ovarian cancer. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm182057.htm. Retrieved September 15, 2010.

60. Ueland F, DeSimone C, Seamon L, Ware R, Goodrich S, Podzielinski I, et al. The OVA1 test improves the preoperative assessment of ovarian tumors. Gynecol Oncol 2010;116:S23.

61. Bailey CL, Ueland FR, Land GL, DePriest PD, Gallion HH, Kryscio RJ, et al. The malignant potential of small cystic ovarian tumours in women over 50 years of age. Gynecol Oncol 1998;69:3–7.

62. Crayford TJ, Campbell S, Bourne TH, Rawson HJ, Collins WP. Benign ovarian cysts and ovarian cancer: a cohort study with implications for screening. Lancet 2000;355:1060–3.

63. Castillo G, Alcázar JL, Jurado M. Natural history of sonographically detected simple unilocular adnexal cysts in asymptomatic postmenopausal women. Gynecol Oncol 2004;92:965–9.

64. Modesitt SC, Pavlik EJ, Ueland FR, DePriest PD, Kryscio RJ, van Nagell JR Jr. Risk of malignancy in unilocular ovarian cystic tumors less than 10 centimeters in diameter. Obstet Gynecol 2003;102:594–9.

65. Greenlee RT, Kessel B, Williams CR, et al. Prevalence, incidence, and natural history of simple ovarian cysts among women 55 years old in a large cancer screening trial. Am J Obstet Gynecol 2010;202:373.e1–9.

66. Scully RE. Early de novo ovarian cancer and cancer developing in benign ovarian lesions. Int J Gynaecol Obstet 1995;49(Suppl):S9–15.

67. Powell DE, Puls L, van Nagell J Jr. Current concepts in epithelial ovarian tumors: does benign to malignant transformation occur? Hum Pathol 1992;23:846–7.

68. Poels LE, Powell De, DePriest PD, Gallion HH, Hunter JE, Kryscio RJ, et al. Transition from benign to malignant epithelium in mucinous and serous ovarian cystadenocarcinoma. Gynecol Oncol 1992;47:53–7.

69. Westhoff C, Clark CJ. Benign ovarian cysts in England and Wales and in the United States. Br J Obstet Gynaecol 1992;99:329–32.

70. Glantz SA. Primer of biostatistics. 6th ed. New York (NY): McGraw-Hill Medical; 2005.

71. Borgfeldt C, Andolf E. Transvaginal sonographic ovarian findings in a random sample of women 25–40 years old. Ultrasound Obstet Gynecol 1999;13:345–50.

72. Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. The Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006134. DOI: 10.1002/14651858.CD006134.pub3.

73. Chiaffarino F, Parazzini F, La Vecchia C, Ricci E, Crosignani PG. Oral contraceptive use and benign gynecologic conditions. A review. Contraception 1998;57:11–8.

74. van Nagell JR Jr, DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. Cancer 2007;109:1887–96.

75. Templeman CL, Fallat ME, Lam AM, Perlman SE, Hertweck SP, O'Connor DM. Managing mature cystic teratomas of the ovary. Obstet Gynecol Surv. 2000;55:738–45.

76. Kondo W, Bourdel N, Cotte B, Tran X, Botchorishvili R, Jardon K, et al. Does prevention of intraperitoneal spillage when removing a dermoid cyst prevent granulomatous peritonitis? BJOG 2010;117:1027–30.

77. Commerci J, Licciardi F, Bergh PA, Gregori C, Breen JL. Mature cystic teratoma: a clinicopathologic evaulation of 517 cases and review of the literature. Obstet Gynecol 1994;84:22–8.

78. Singh P, Yordan E, Wilbanks G, Miller AW, Wee A, et al. Malignancy associated with benign cystic teratomas (dermoid cysts) of the ovary. Singapore J Med 1988;29:30–4.

79. Erzen M, Rakar S, Klancnik B, Syrjänen K, Syrjänen K, Klancar B. Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct from other ovarian carcinomas as suggested by a nested case-control study. Gynecol Oncol 2001;83:100–8.

80. Medeiros LR, Fachel JM, Garry R, Stein AT, Furness S. Laparoscopy versus laparotomy for benign ovarian tumours. The Cochrane Database of Systematic Reviews 2005, Issue 20. Art. No.: CD004751. DOI: 10.1002/14651858.CD004751.pub3.

81. Teplin V, Vittinghoff E, Lin F, Learman LA, Richter HE, Kuppermann M. Oophorectomy in premenopausal women: health-related quality of life and sexual functioning. Obstet Gynecol 2007;109(2 Pt 1):347–54.

82. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 2006;7:821–8.

83. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol 2003;21:1180–9.

84. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. Gynecol Oncol 1994;55(3 Pt 2): S62–72.

85. Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. J Clin Oncol 2007;10:25:2928–37.

86. Medeiros LR, Rosa DD, Edelweiss MI, Stein AT, Bozzetti MC, Zelmanowicz A, et al. Accuracy of frozen-section analysis in the diagnosis of ovarian tumors: a systematic quantitative review. Int J Gynecol Cancer 2005;15:192–202.

87. Geomini PM, Zuurendonk LD, Bremer GL, de Graaff J, Kruitwagen RF, Mol BW. The impact of size of the adnexal mass on the accuracy of frozen section diagnosis. Gynecol Oncol 2005;99:362–6.

88. Brun JL, Cortez A, Rouzier R, Callard P, Bazot M, Uzan S, et al. Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumors. Am J Obstet Gynecol. 2008;199:244.e1–7.

89. Elit L, Bondy SJ, Paszat L, Przybysz R, Levine M. Outcomes in surgery for ovarian cancer. Gynecol Oncol 2002;87:260–7.

90. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer 2006;106:589–98.

91. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? Gynecol Oncol 2002;84:36–42.

92. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. ACOG Committee Opinion No. 280. American College of Obstetricians and Gynecologists. Obstet Gynecol 2002;100:1413–6.

93. Society of Gynecologic Oncologists. Guidelines for referral to a gynecologic oncologist: rationale and benefits. Gynecol Oncol 2000;78:S1–13.

94. Dearking AC, Aletti GD, McGree ME, Weaver AL, Sommerfield MK, Cliby WA. How relevant are ACOG and SGO guidelines for referral of adnexal mass? Obstet Gynecol 2007; 110:841–8.

95. Cronje HS, Niemand I, Bam RH, Woodruff JD. Review of the granulosa-theca cell tumors from the Emil Novak Ovarian Tumor Registry. Am J Obstet Gynecol 1999;180:323–7.

96. Schmeier KM, Gershenson DM. Low-grade serous ovarian cancer: a unique disease. Curr Oncol Rep 2008;10:519–23.

97. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–30.