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Imaging and Differential Diagnosis of Ovarian Cancer

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Ovarian cancer is the seventh most common cancer affecting women. Despite advances in cancer control and healthcare in general, mortality from ovarian cancer remains unacceptably high due to diagnosis at an advanced stage of the disease. The 5-year survival rate is 47.4% because a majority of ovarian cancers are diagnosed when advanced. Only 14.9% of ovarian cancers are diagnosed when localized where the survival rate is 92.3%. Mortality rate reduction by screening has not been proven in women at an average risk for ovarian cancer. Ultrasound remains the primary modality for assessment of ovarian tumors. The need for standardizing terminology is critical for optimal assessment of the risk of malignancy in an ovarian tumor. The international ovarian tumor analysis group and more recently the American College of Radiology Ovarian – Adnexal Reporting and Data System Committee have published standardized lexicon for ovarian lesions and encourage ultrasound imagers to adopt this standardized terminology. The aim is to apply the lexicon for risk stratification to allow for consistent follow-up and management. Various methodologies have been tested for characterization of adnexal tumors and to assess risk of malignancy preoperatively. Risk assessment models have been studied against the gold standard of a pattern recognition approach and subjective assessment by an experienced imager. The morphologic patterns of ovarian tumors are detailed and features that are more discriminatory than others in suggesting an ovarian malignancy are described. The imaging pathologic correlation for different tumor types is presented. A brief summary of the ovarian cancer pathologic types and staging of cancer is presented. Finally, the current role of transvaginal sonography as a screening modality for ovarian cancer is discussed. Recently published data show encouraging results, that a multimodal approach of screening for ovarian cancer using transvaginal sonography in women with an elevated CA-125 may prove beneficial and cost effective.

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Introduction

Ovarian cancer causes more deaths than any other cancer of the female reproductive system. It is the fifth most common cause of cancer deaths among women. About half of the women who are diagnosed with ovarian cancer are 63 years or older. Based on the surveillance, epidemiology, and end results data provided by the National Cancer Institute there were an estimated 22,240 new cases of ovarian cancer in 2018 accounting for 1.3% of all new cancer cases. Estimated deaths were 14,070 representing 2.3% of all cancer deaths. The 5-year survival rate was only 47.4%. The number of new cases of ovarian cancer was 11.6 per 100,000 women and the number of deaths was 7.2 per 100,000 women. These are age adjusted and based on data from 2011 to 2015. The life time risk of developing ovarian cancer is 1.3%. In 2015 there were an estimated 224,940 women with ovarian cancer in the United States. Five-year survival drops from 92.3% for cases confined to the ovary to a dismal 29.2% in patients with distant metastasis. Unfortunately, despite advanced in medicine, 59% of women with ovarian cancer are diagnosed after the cancer has metastasized.[1-2]

Ovarian Tumors: Malignancy Risk Stratification

A risk of malignancy assessment of an ovarian tumor is a prerequisite to plan an appropriate course of management.

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Adnexal tumors that are considered likely nonneoplastic are managed conservatively, benign ovarian tumors are managed expectantly or with laparoscopic surgery. Tumors with a higher likelihood of being malignant are best managed at a specialized hospital with involvement of a gynecologic oncologist; these patients also undergo additional imaging with CT or MRI to assess extent of disease for the purpose of preoperative staging. Several methods have been proposed for a preoperative assessment of the risk of malignancy of an adnexal tumor. These are described below and include a pattern recognition approach, the International Ovarian Tumor Analysis (IOTA) groups mathematical logistical regression models, simple ultrasound-based rules for diagnosis of ovarian cancer, risk of malignancy index (RMI) models and the Gynecological Imaging Reporting and Data systems (GI-RADS).

Pattern Recognition Approach

A pattern recognition approach or subjective assessment of an ovarian tumor based on sonographic morphology and Doppler assessment of vascularity remains the gold standard in the preoperative risk of malignancy assessment. The accuracy of such an assessment has been shown to be dependent on the expertise of the examiner.[3] In a pattern recognition approach, ovarian tumors are placed in 1 of 5 groups, unilocular cyst, unilocular solid cyst, multilocular cyst, multilocular solid cyst, and a solid tumor[4] (Fig. 1A-E). Risk of malignancy is then assessed based on ultrasound morphology and Doppler imaging characteristics. This approach works well with experienced ultrasound imagers. In a prospective study of 300 ovarian tumors that underwent surgery, the accuracy of preoperative diagnosis based on a subjective assessment was 92% for experienced imagers and significantly lower for less experienced operators at 82%-87%. Experienced imagers had a sensitivity of 96% and a sensitivity of 90% in the assessment of ovarian tumors[3]

IOTA Logistical Regression Models

The International Ovarian Tumor Analysis (IOTA) group developed a logistical regression model to preoperatively assign malignancy risk to ovarian tumors in patients undergoing surgery. In a multicenter trial including 1066 patients, in whom there were 800 benign tumors (75%) and 266 malignant tumors (25%) a sensitivity of 93% and a specificity of 76% were reported.[5] The IOTA group subsequently carried out a study in 507 patients to internally validate the mathematical models to estimate risk of malignancy in adnexal tumors. The accuracy was found to be similar to that in the original data set. Diagnostic performance compared well to the superior pattern recognition approach by expert sonologists.[6] The 11 mathematical models that had been originally developed were applied for validation in a prospective study.[5] Sensitivity and specificity of all IOTA models ranged from 92% to 94% and from 74% to 84%, respectively compared to a sensitivity and specificity of 90.2% and 92.9% with a pattern recognition approach.[5]

Simple Ultrasound-based Rules for the Diagnosis of Ovarian Cancer

The value of applying simple and clinically useful ultrasound features-based methodology to discriminate between benign and malignant tumors has also been studied. In 1066 patients with 1233 adnexal tumors, 903 of which were benign tumors (73%) and 330 were malignant tumors (27%), 5 simple rules were used to predict malignancy. An irregular solid tumor; presence of ascites; 4 or more papillary structures, an irregular multilocular-solid tumor with a largest diameter of at least 100 mm; and a very high color content on color Doppler examination. Features of a benign tumor included presence of a unilocular cyst, solid components <7 mm in largest diameter, presence of acoustic shadows, a smooth multilocular tumor less than 100 mm in largest diameter, and no detectable blood flow on Doppler examination. Based on the simple ultrasound rules it was shown that 76% of the tumors could be classified. This resulted in a sensitivity of 93% and specificity of 90%. It was suggested that for those tumors that could not be classified by the simple rules, subjective assessment by an expert examiner was utilized.[7]

IOTA ADNEX Model for Characterization of Different Types of Ovarian Cancers

The IOTA group has also developed a risk prediction model for a more detailed characterization of adnexal masses called assessment of different neoplasias in the adnexa (ADNEX model). The 3 clinical and 6 ultrasound features were used to predict the risk of a benign ovarian tumor, a borderline ovarian tumor, Stage I ovarian cancer, and Stage II-IV ovarian cancer and metastasis. The clinical features used included, age of the patient, CA 125 level, type of center managing the patient (oncology centers vs other hospitals), family history of ovarian cancer, maximum diameter of lesion, proportion of solid tissue, more than 10 cyst locules, number of papillary projections, acoustic shadows, and ascites. The study included 3506 women with an adnexal mass who underwent a standardized ultrasound examination preoperatively. The model was developed on these patients and temporally validated on 2403 patients and then updated on all 5909 patients. The ADNEX model was found to do well in distinguishing benign from malignant tumors and fair to excellent in discriminating between the 4 types of ovarian cancers, namely Borderline and Stage I and Stage I and Stage II-IV ovarian cancers and metastasis. The ADNEX model could assist in triaging the patients and make appropriate management decisions that have the potential to reduce mortality and morbidity.[8] These findings have been validated by others with encouraging results.[9,10] In a series of 131 women, with 63 benign, 16 BOT and 17 Stage I and 24 with Stage II-IV ovarian cancer and 11 with ovarian metastasis. The IOTA ADNEX model did well in differentiating between benign

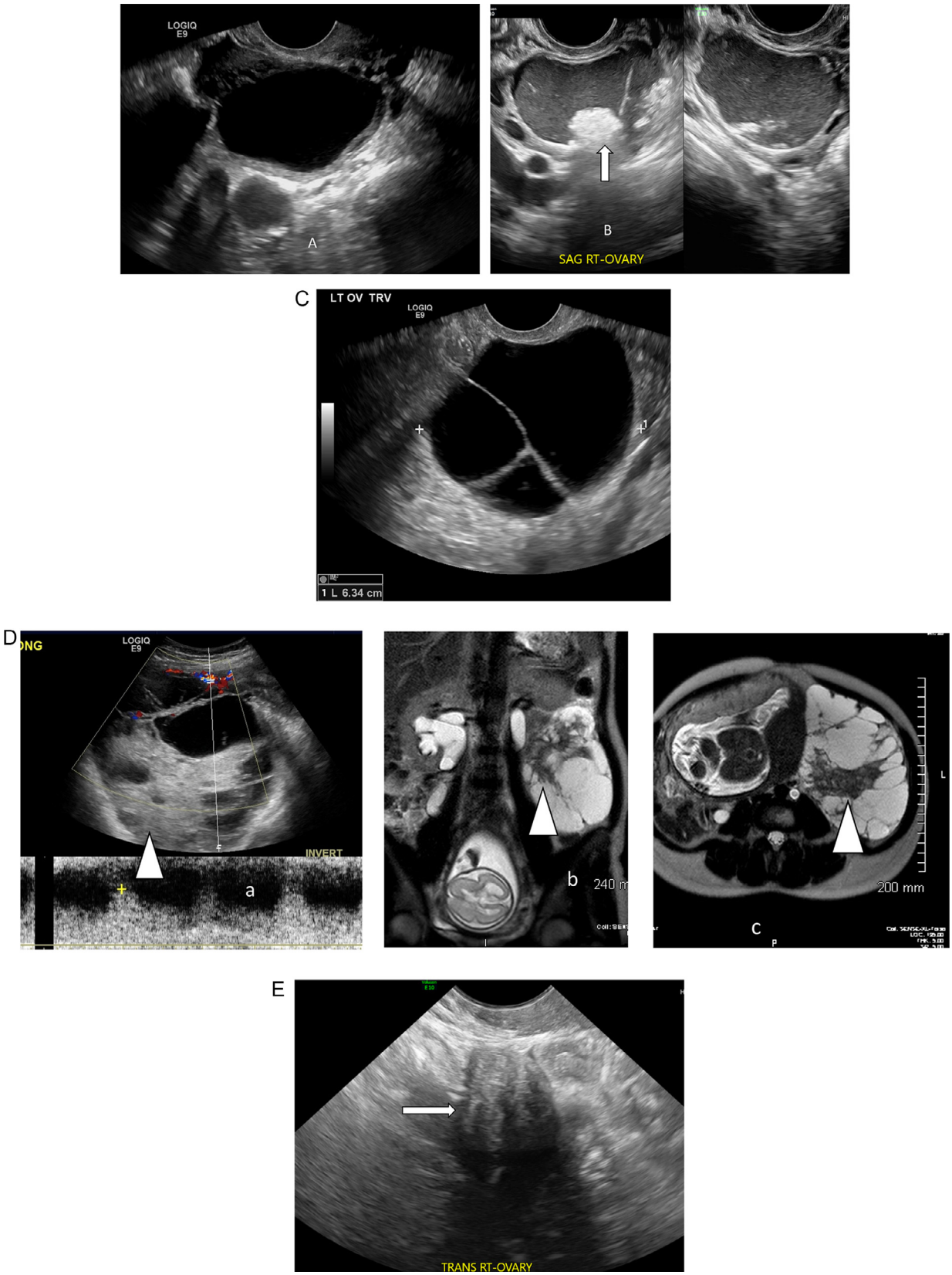

Figure 1 (A) Unilocular cyst. (B) Unilocular solid mass. A unilocular cyst with mixed echogenic internal contents and a solid component (arrow) with shadowing characteristic of a dermoid. (C) Multilocular cyst without solid components. A cystic adnexal tumor with multiple complete septations. (D) Ultrasound (a) and T2-weighted coronal (b) and axial MRI(c) images of a multiloculated cystic mass with solid components (arrowheads) surgically proven to be a yolk sac tumor in a pregnant woman. (E) Solid tumor of the ovary (arrow) with multiple areas of acoustic shadowing proven to be a fibroma.

and Stage II-IV, BOT and Stage II-IV, and Stage I against I-IV. The risk prediction models did not do well in discriminating between BOT and Stage I ovarian cancer and between Stage I cancer and ovarian metastasis.[9] More recently the IOTA ADNEX model as a risk prediction model was shown to be useful in discriminating benign from malignant masses based on ultrasound features in a series of 93 postmenopausal women with ovarian tumors. A combination of the 2 methods showed a sensitivity and specificity rates of respectively 100% and 98%, a negative predictive value (NPV) of 100% and a positive predictive value (PPV) of 80%.[10]

The scoring systems and mathematical models such as the IOTA simple ultrasound-based rules, IOTA regression model 2 (LR2) come closest to the accuracy of subjective assessment by expert examiners with an advantage over the latter of being able to be used by less experienced examiners.[11] A systematic review and meta-analysis was undertaken to compare the accuracy of a subjective assessment and the ultrasound models in discriminating benign from malignant ovarian malignancies. The meta-analysis included 19,674 tumors, 13,953 (70.99%) benign, and 5721 (29.1%) malignant. Subjective assessment using pattern recognition by expert examiners had the best accuracy. A 2-step strategy of simple rules with subjective assessment for inconclusive tumors performed well and matched test performance of expert ultrasound examiners. The IOTA LR2 model uses 6 variables compared to the 12 used in the LR1 model. These include age, ascites, blood flow within papillary projection, maximum diameter of the solid component, irregular cyst wall, and acoustic shadows.[11] The IOTA LR2 model also seems a good alternative method in the absence of an experienced expert ultrasound imager.

Risk of Malignancy Index

The RMI is another scoring system to preoperatively assign ovarian masses into benign or malignant groups. RMI is based on the ultrasound features, the menopausal status, and CA 125 levels. The menopausal status is based on at least 1 year of amenorrhea or a woman older than 50 years who had undergone a hysterectomy. The imaging score is based on features suggestive of malignancy such as solid areas, multilocularity, bilaterality, ascites, and intra-abdominal metastasis, with 1 point assigned to each of these scores. Each tumor is assigned a final score that is calculated as a product of the imaging score, menopausal status, and CA 125. An ultrasound score of 0 or 1 yielded $U = 1$, a score equal to or greater than 2 yielded a score of $U = 4$, premenopausal yielded a score of 1, and postmenopausal $M = 4$, the serum level of CA 125 was directly applied to the equation. There are 4 RMI models. RMI 4 took into consideration the size of the tumor, one larger than 7 cm was assigned a score of 2. RMI models 2 and 3 differed in the score assigned to each component. RMI 2 performed the best among these models with a sensitivity of 81.1% and a specificity of 89.6%. The RMI models were not as accurate as the pattern recognition by an experienced imager[12]

Adnexal Tumors Difficult to Classify

About 7%-10% of ovarian tumors are not able to be classified as benign or malignant based on a pattern recognition approach even by experienced imagers.[3,13,14] Use of logistical regression models, RMI, and CA 125 measurements were also not found to be useful in such unclassified tumors. Borderline tumors have been shown to the most difficult to assess with only 47% being assigned as being malignant.[14] Papillary cystadenofibromas, myomas, and struma ovarii were more common in the unclassifiable masses. Subjective assessment fared poorly with a sensitivity of 56% (14/25) and a specificity of 77% (50/65).[14] The incidence of malignancy can be significant in the unclassifiable tumors (30%).[13] Multilocular cysts with more than 10 locules and masses with small solid components seem to be particularly challenging.[13]

Gynecological Imaging Reporting and Data System

A reporting system was proposed and developed that classified adnexal masses and studied on 187 masses. The GI-RADS is a way to classify adnexal masses based on transvaginal sonographic appearance. The purpose was to standardize reporting in a meaningful way that would help referring clinicians appropriately manage patients based on the risk of malignancy. GI-RADS 1 class was definitively benign with normal ovaries, GI-RADS 2 was for very probably benign lesions and included functional cysts and hemorrhagic cysts, GI-RADS 3 was for probably benign lesions and included dermoids, endometriomas, and paraovarian cysts, GI-RADS 4 was assigned to probably malignant ovarian tumors, and GI-RADS 5 represented very probably malignant tumors (Fig. 2A-E). GI-RADS 1 and 2 are managed conservatively, 3, 4, and 5 are managed surgically. In the study group there were 13.4% malignant tumors. The sensitivity, specificity, PPV, NPV, and an accuracy of 92%, 97%, 85%, 99%, and 96%, respectively was achieved.[15] Others have shown that this system does well and addition of CA 125 improves accuracy. For GI-RADS 4 and 5 lesions, the sensitivity, specificity, PPV, NPV, Accuracy, and Odds ratio were as follows: 94.3%, 72.2%, 52.6%, 97.5%, 77.7%, and 43.3 (confidence interval 12.0-146), respectively. The corresponding parameters resulting from combining the GI-RADS classification with the CA-125 marker were as follows: 66.0, 93.8, 77.8, 89.4, and 87.0%.[16] In a series of 263 adnexal masses GI-RADS was found to do well in classifying ovarian tumors using this risk stratification method. The GI-RADS classification performed well in the diagnosis of malignant adnexal masses. The sensitivity, specificity, false-positive rate, false-negative rate, and accuracy for the GI-RADS classification were 96.4%, 84.3%, 18.5%, 3.0%, and 89.3%, respectively.[17]

Ovarian Tumor Lexicon

Lack of standard terminology to describe morphologic features of adnexal tumors has led to variable interpretation resulting in suboptimal management strategies. The Breast

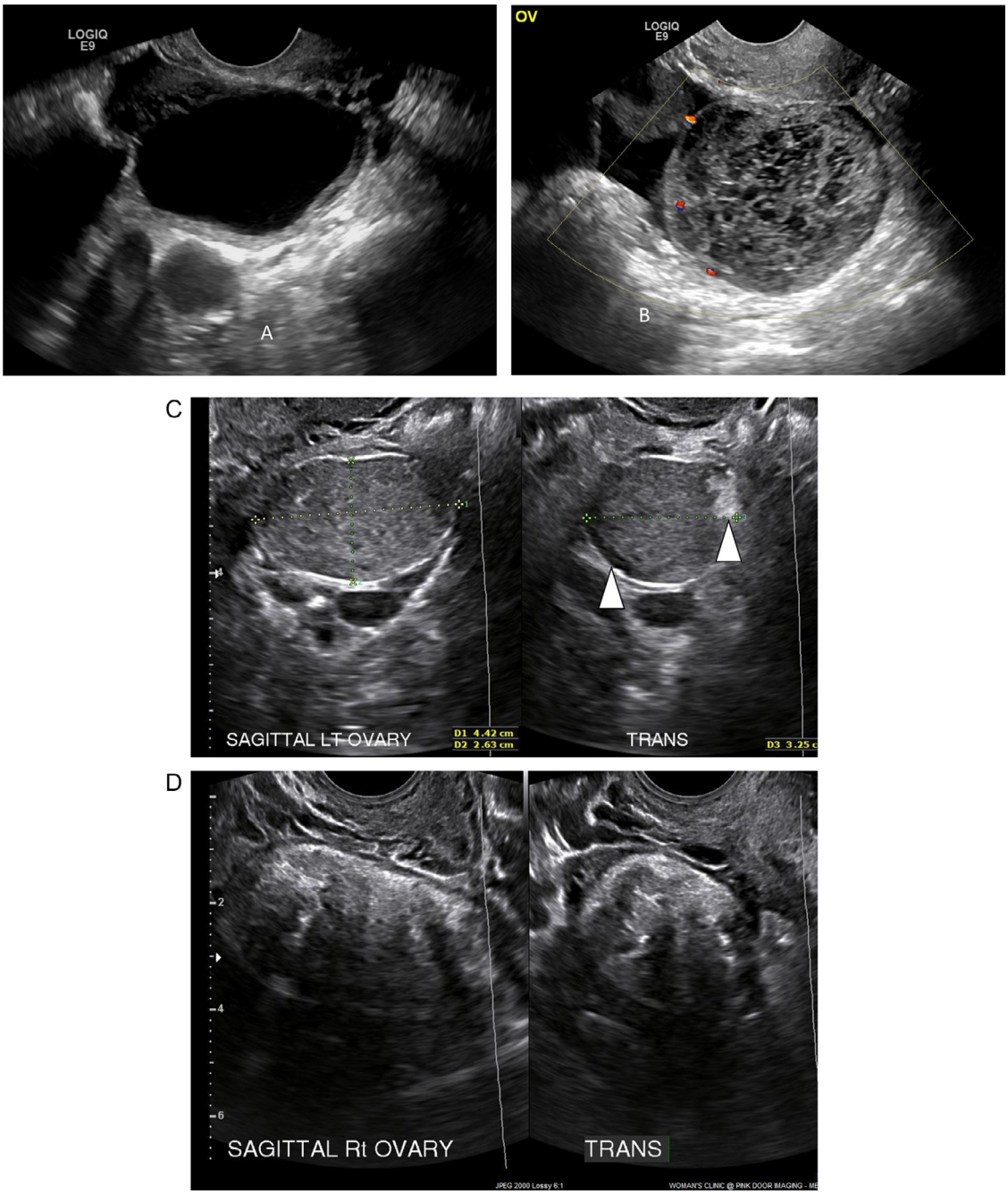

Figure 2 GI-RADS 2 very probably benign. (A) Simple unilocular cyst that resolved at follow-up (not shown). (B) A unilocular cyst with lace like internal echoes consistent with a hemorrhagic cyst. (C) GI-RADS 2. Very probably benign. Unilocular cyst with compact internal echoes with hyperechoic component (arrowhead) and a peripheral curvilinear lucency (arrowhead) suggestive of an endometrioma. (D) GI-RADS 3. Probably benign. A solid ovarian tumor with hyperechogencities and posterior acoustic shadowing. (E) GI-RADS 5. Very probably malignant. Ultrasound shows a large predominantly solid mass with ascites. (F) GI-RADS 4. Probably malignant. Real time and color Doppler images demonstrate a unilocular cyst with a large solid component demonstrating moderate vascularity within the solid component.

Imaging and Reporting Data system was implemented and has been successful in standardizing reporting in breast imaging.[18] A similar need exists to standardize the descriptors of B-mode and Doppler imaging characteristics of adnexal tumors. The IOTA group was an initiative launched in Europe to establish a standardized lexicon for adnexal lesions and to establish terms and mechanisms to derive morphologic end points based on findings on B-mode imaging and Doppler evaluation of adnexal pathology.[19] More recently the American College of Radiology established a committee charged with creating a standardized lexicon for ovarian lesions with the purpose of improving

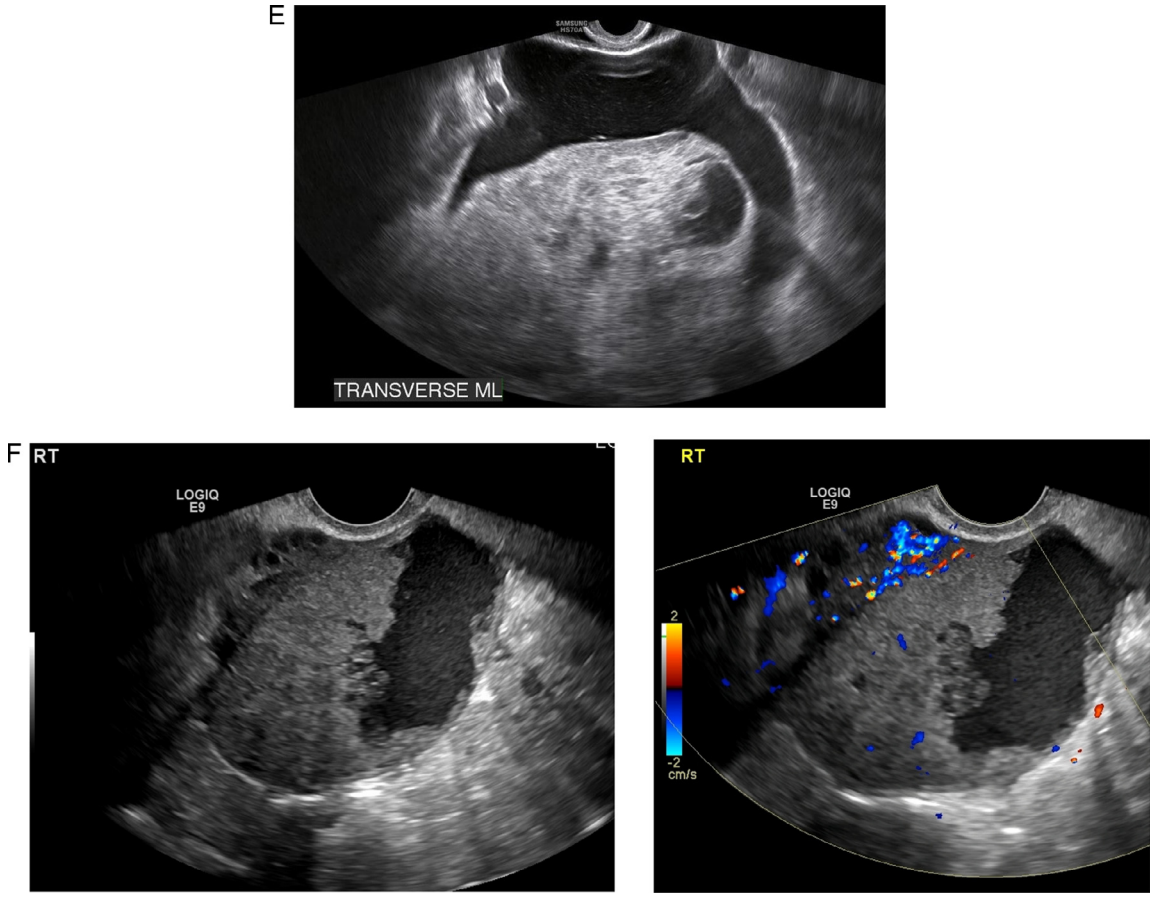

Figure 2 Continued.

communication of imaging findings and reporting to the referring clinicians thereby allowing them to make optimal management decisions. The ultimate goal was to apply such a lexicon to a risk stratification classification for consistent follow-up and management in clinical practice.[20] Ovarian tumors are broadly categorized based on predominant morphology either cystic or solid (Table 1).

Cystic Tumors of the Ovary

A cystic tumor is further subclassified. Septa can be complete and incomplete. Cysts with incomplete septation are considered unilocular. Presence of a complete septum makes the cystic adnexal mass multilocular (Fig. 3). The cystic contents are described as anechoic, low level echoes as seen in mucinous cystadenoma, a more ground glass compact internal echoes as seen in an endometrioma (Fig. 4), and lacy thread like or cob web like, as in a hemorrhagic cyst, in these cases gentle pressure with the endovaginal probe causes the blood products to move in real time. Mixed echogenicity as seen in a dermoid. The internal wall of a cyst is described as smooth or irregular. Papillary projections and solid components when present make the internal wall irregular (Fig. 5). Solid papillary projections are any solid component projecting into the cyst that is equal to or greater than 3 mm in height. Sometimes an incomplete septum may be difficult to distinguish from a papillary projection.[19]

Solid Tumors of the Ovary

When a tumor has greater than 80% echogenic solid component it is considered as a solid mass (Figs. 6-8). A septum, wall thickening of a cyst is not considered as a solid component. Presence of vascularity confirms a solid mass, absence of blood flow is not helpful. Distinction from a blood clot may be difficult particularly in an endometrioma, in these cases internal movement observed in real time on gentle pressure with the transducer is helpful in confirming a blood clot. The external surface of a solid mass is described as being smooth or irregular.[19,20]

Measurement

The ovary and the tumor are measured at its largest dimension in two perpendicular planes. Presence of ascites is documented and the fluid in the pouch of Douglass is measured in the sagittal anteroposterior plane at the maximum depth. The septation is measured at its maximum thickness. The papillary projection or the solid component of a cystic tumor is measured in three dimensions in two perpendicular planes. The number of locules is documented in multiloculated tumors.[19]

Vascular Features of Ovarian Tumors

The entire tumor is evaluated with both color and spectral Doppler. A color doppler score is given based on the amount

Table 1 Ovarian Tumor Descriptors[19]

Solid Tumor (>80% solid)	Cystic Tumor
• External surface	• Internal septations in a cystic mass
• Presence of acoustic shadow	➢ Unilocular (no complete septation)
• Doppler assessment	➢ Multilocular (at least one omplete septation)
➢ Color Doppler score[1-4]	• Internal wall of a cystic mass
➢ Spectral Doppler: PSV, RI, PI	➢ Smooth
	➢ Irregular
	Papillary projections, solid components
	• Internal contents
	➢ Anechoic
	➢ Low level internal echoes
	➢ Ground glass (as in an endometrioma)
	➢ Hemorrhagic
	➢ Mixed echogenicity (as in a dermoid)
	• Doppler assessment
	➢ Color Doppler score[1-4]
	➢ Spectral Doppler: PSV, RI, PI

of vascularity, a score of 1 when there is no flow, 2 when there is minimal flow, 3 when there is moderate flow, and 4 when the mass is very vascular (Figs. 9-12). When multiple areas of vascular flow are present, a spectral Doppler assessment of the highest time averaged maximum velocity, and corresponding peak systolic velocity, pulsatility index (PI), and resistive index (RI) is selected.[19,20]

Ovarian Tumors: Morphologic Patterns

Unilocular Cyst

A unilocular cyst is a cystic lesion with a single compartment that may contain an incomplete septum or solid element less than 3 mm. A unilocular cyst with a smooth internal wall has been shown to have an extremely low likelihood of malignancy and reported to vary from 0.3% to 1.1%.[21-24] Malignancy rate is higher in postmenopausal women and with larger cysts. A majority of the malignancies found in unilocular tumors are borderline tumors of the ovary (BOT).[22-24] In a series of 296 malignant tumors there was only one 5 cm unilocular cyst (0.3%) in a 60-year-old woman that was malignant, the cyst had irregular internal wall.[21] Up to a third of adnexal tumors undergoing surgical excision are unilocular cysts, the malignancy rate is lower in premenopausal women (0.54%) and higher in postmenopausal women (2.6%).[22] In large unilocular cysts ultrasound may fail to detect small papillary projections even when present that are subsequently identified in surgical specimens. Hemorrhagic cyst contents are more common in malignant unilocular cysts (18% vs 2%).[22] In 7 of 11 malignancies, papillary projections were seen at macroscopic inspection of the surgical specimen. A similar low malignancy rate was observed in a meta-analysis of unilocular cysts undergoing surgery, 1.1% in a series of 2177 unilocular cysts. About 0.6% of the unilocular cysts were borderline malignant. The malignancy rates were lower in premenopausal women (0.6%) than in postmenopausal women (3.2%). When cyst contents were anechoic the malignancy rate was 0.9%, a third of these were borderline malignant tumors.[23] In a prospective study of 927 premenopausal women and 377 postmenopausal women undergoing surgical removal of a unilocular cyst, the malignancy rate in premenopausal women with anechoic cyst contents and no wall irregularity or solid components was 0.73%. And in postmenopausal women was 1.6%. When cyst contents were echogenic, and with solid parts or papillations, the malignancy rate in premenopausal women was 2.1% and in the postmenopausal group was 10%. It may therefore be prudent to follow unilocular cyst smaller than 5 cm given the very low malignancy rate.[24]

Unilocular Cyst With Solid Components

A unilocular cyst with a solid component that is greater than 3 mm in height, including papillary projections into the cyst. There is a wide range in the malignancy rate in unilocular cysts with a solid component varying from 2% to 35%.[7,21,24-26] The range reflects the spectrum of the findings that can vary depending on the size of the solid component, internal cyst content, size of the tumor, and the menopausal state of the women. The risk of malignancy increases with height of the largest papillation, confluence of the papillations and presence of vascular flow, and decreases when there is posterior acoustic shadowing associated with the papillations. In a series of 204 unilocular cysts with solid elements, the malignancy rate was 35.3% (20.6% borderline and 14.7% primary invasive cancers) and 64.2% were benign.[26] In a series of 644 cysts among a total of 1304 cysts that had echogenic internal contents and solid parts or papillations. About 2.1% of such cysts in the premenopausal group and 10% of the cysts in the postmenopausal group were borderline or malignant.[24] In another series of 3511 adnexal masses, there were 252 tumors (7%) with unilocular solid cysts with papillations. The malignancy rate in this series in this group was 35.4%, among these 15.9% were borderline malignant tumors, 17.1% primary invasive tumors, and 2.4% metastasis. Majority of the primary invasive tumors were Stage I ovarian malignancies (24/43).[25]

Multilocular Cyst

A multilocular cyst is a cystic adnexal tumor with at least 1 complete septum. The malignancy rate in multilocular cyst without solid elements is low and ranges from 8% to 10.3%.[4,8] Multilocular cysts were malignant in 8% (20/229) in one study with a larger percentage of the benign tumors

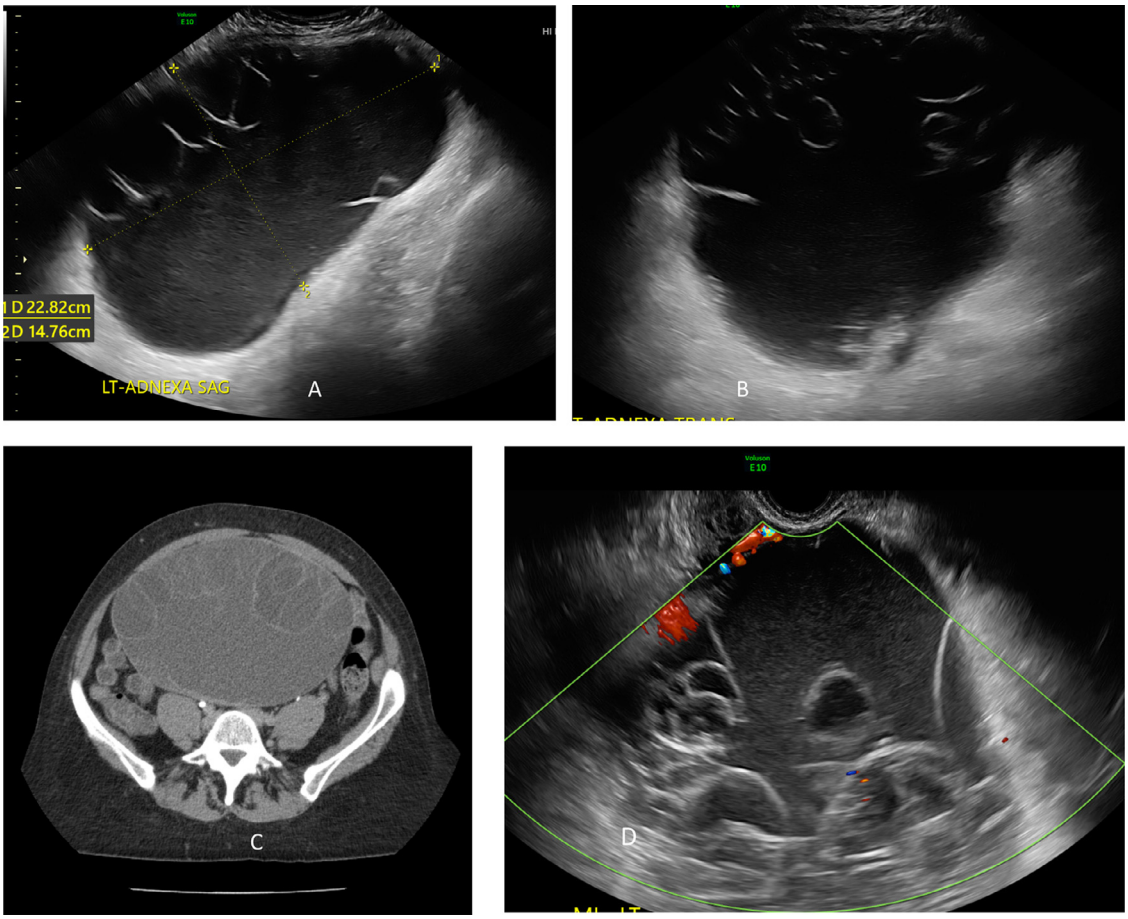

Figure 3 Large multiloculated cystic ovarian tumor without solid components and minimal vascular flow. There was no associated ascites. Surgical diagnosis was a borderline mucinous cystadenoma. (A) Sagittal and (B) transverse ultrasound images. (C) Axial CT scan image. (D) Color Doppler score of 1 with no flow observed within the septations.

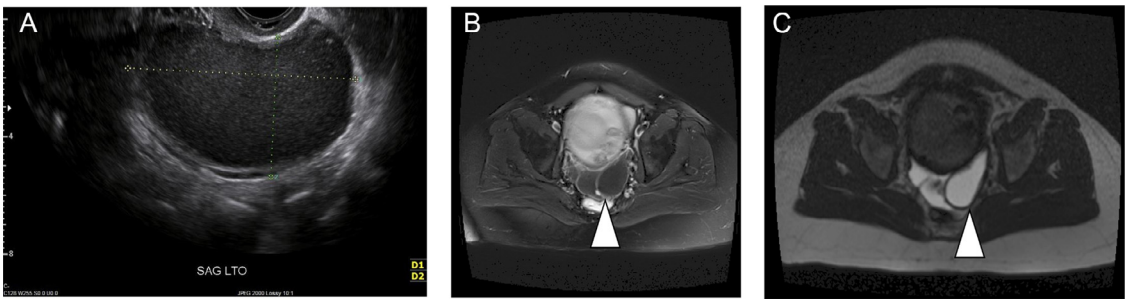

Figure 4 Cystic ovarian tumors. (A) Unilocular cystic tumor with compact internal echoes and a thick wall. (B) Axial T1-weighted postcontrast image demonstrates an enhancing wall. (C) T1-weighted axial image demonstrates a cystic mass (arrowhead) with high signal internal contents and a low signal intensity rim characteristic of an endometrioma. The diagnosis of an endometrioma was confirmed at surgery performed because of the patient's symptoms.

appearing as a multilocular cyst (22%) compared to malignant ovarian tumors (7.5%).[21] Others have reported similar results with a PPV of this appearance in an ovarian tumor for malignancy of 10.3% (22/213). A multilocular cyst is seen much less commonly in malignant tumors (6.7%-22/330).[7] A higher percentage of malignant tumors appeared as multilocular cyst in the IOTA study group where among 326 adnexal tumors, 33.6% of benign tumors, and 22.1% of borderline malignant tumors presented as multilocular cysts, with no invasive cancers.[8]

Multilocular Cyst With Solid Components

Multilocular cyst with solid component is a cystic tumor with at least 1 complete septum and a solid component greater than 3 mm in height.[19] Malignancy rate for multilocular solid tumors is generally high and ranges from 36% to 43%.[5,8,21] In 1 series the PPV of malignancy in a multilocular cyst with solid components was 43% (139/323). Such an appearance was seen in 42.1% of malignant tumors (139/330) and 20.4% (184/ 903) of benign tumors. The malignancy rate was 36% in another series (147/209).[7] About 43.6% of

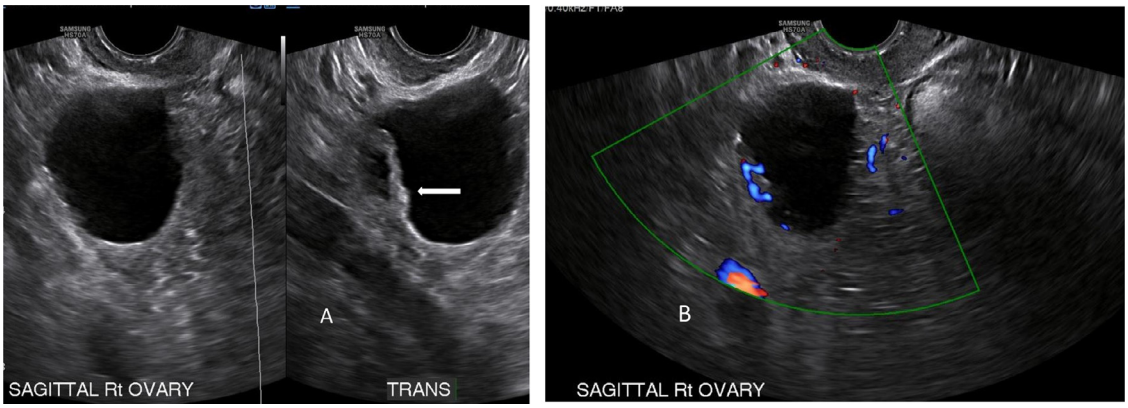

Figure 5 (A) Unilocular cystic right ovarian tumor with solid components (arrow). (B) Color Doppler image shows moderate vascular flow within the solid components.

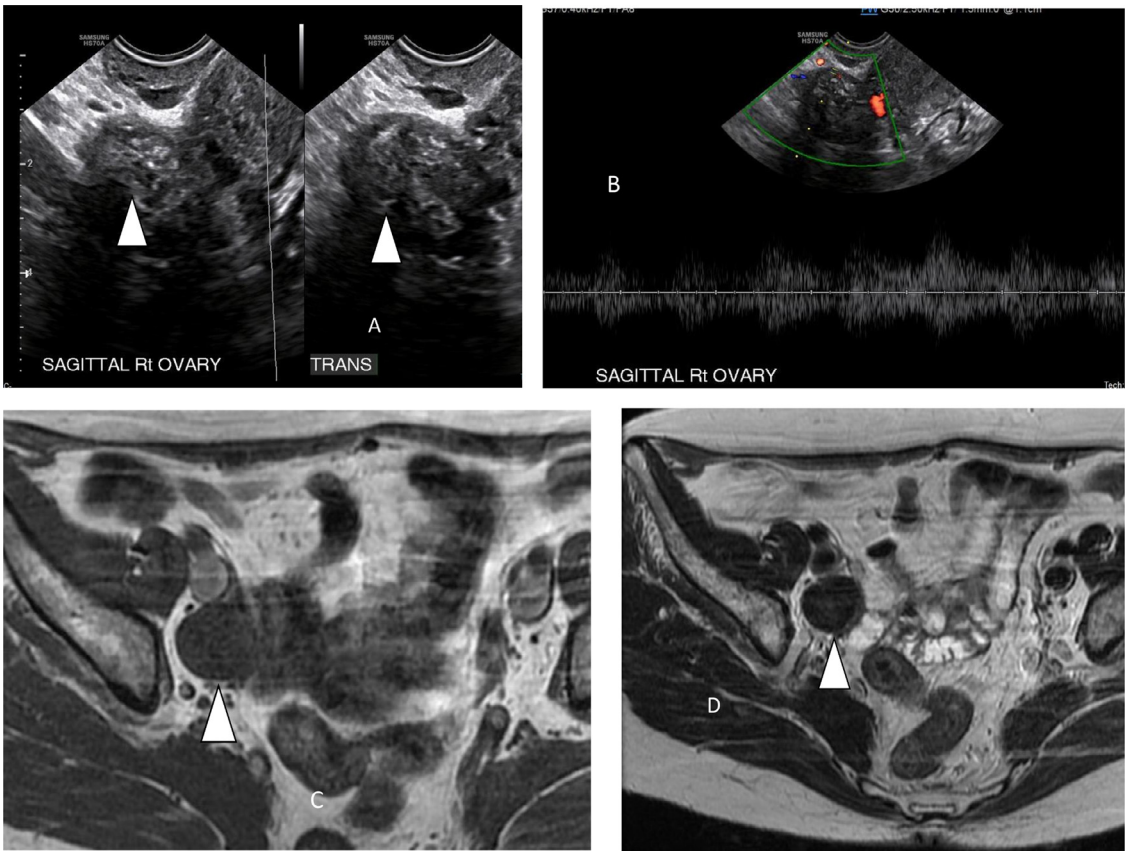

Figure 6 Solid ovarian tumor. Ultrasound image demonstrates a solid tumor of the ovary with a heterogenous echotexture and focal hyperechogencities (A). Color Doppler score of 1 within the tumor. Flow was observed within surrounding ovarian tissue (B). Axial T1-weighted image demonstrates a round solid mass of intermediate to low signal intensity (arrow-head in C) and T2-weighted axial image shows low signal (arrow-head in D). Surgical diagnosis was Brenner's tumor of the ovary.

malignant tumors were multilocular cysts with solid components compared to 21.1% of benign tumors.[5] In a series of 326 adnexal tumors, 59.3% of borderline ovarian malignancies, 61.1% of Stage I, 37.5% of Stage II-IV, and 28.6% of metastatic tumors presented as multilocular cysts with solid components.[8]

Solid Ovarian Tumors

A solid tumor is when 80% of the tumor is composed of solid elements in two planes. The echogenicity of the lesion provides a clue to the component tissue. A lesion that is purely solid is a subset of the solid lesion with no cystic component. The malignancy rate of solid tumors is 39%.[21]

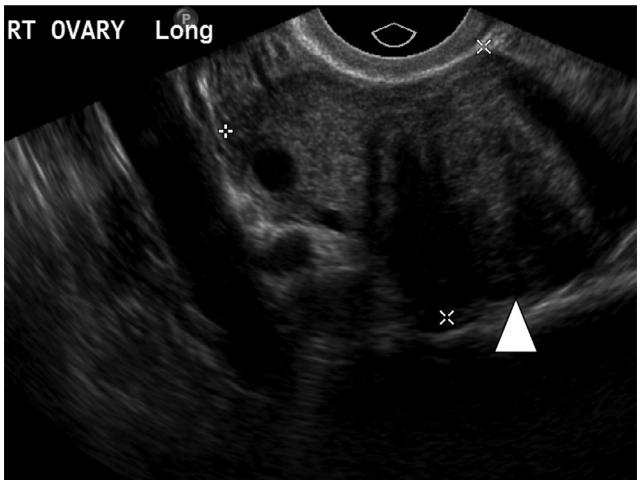

Figure 7 Solid ovarian tumor. Ultrasound image showing a round solid mass with areas of posterior acoustic shadowing (arrow head). Surgical diagnosis was an ovarian fibroma.

In 1 study the PPV of a solid ovarian tumor was 65.3% (111/170), 33.6% of malignant tumors were solid masses, and 6.6% of benign tumors.[7] Solid tumors when malignant are more likely to represent advanced stage cancers. In 1 study 27.8% of Stage I, 55.4% of Stage II-IV, and 64.3% of metastatic tumors were solid adnexal tumors. None were Borderline malignant tumors. Only 9.5% of benign tumors appeared as solid masses.[8]

Imaging Pathologic Correlation of Ovarian Cancers

Borderline Tumors of the Ovary

BOTs are epithelial tumors of the ovary that have a low malignant potential and are prognostically and from a management perspective distinct from ovarian carcinoma. About 75% of these tumors are confined to the ovary with a 10-year survival rate of 97%. Unlike invasive ovarian malignancies, stromal invasion is absent although serous type of BOT that accounts for 50% of such tumors can have peritoneal or lymph node metastasis. About 45% of the nonserous types include mucinous type, with 5% representing endometroid, clear cell, Brenner's tumors.[27] In a series of 37 BOT larger than 5 cm, the sensitivity, specificity, PPV, NPV, and accuracy for combined analysis of MRI with CA 125 was 89.1% 91.9%, 86.8%, 93.4, and 90.9%, respectively.[28] Papillary projections into a cyst cavity are small soft tissue excrescences measuring 1-15 mm in height and 1-10 mm in width and base. Intracystic papillae were the only independent predictors of a borderline ovarian tumor and are seen in

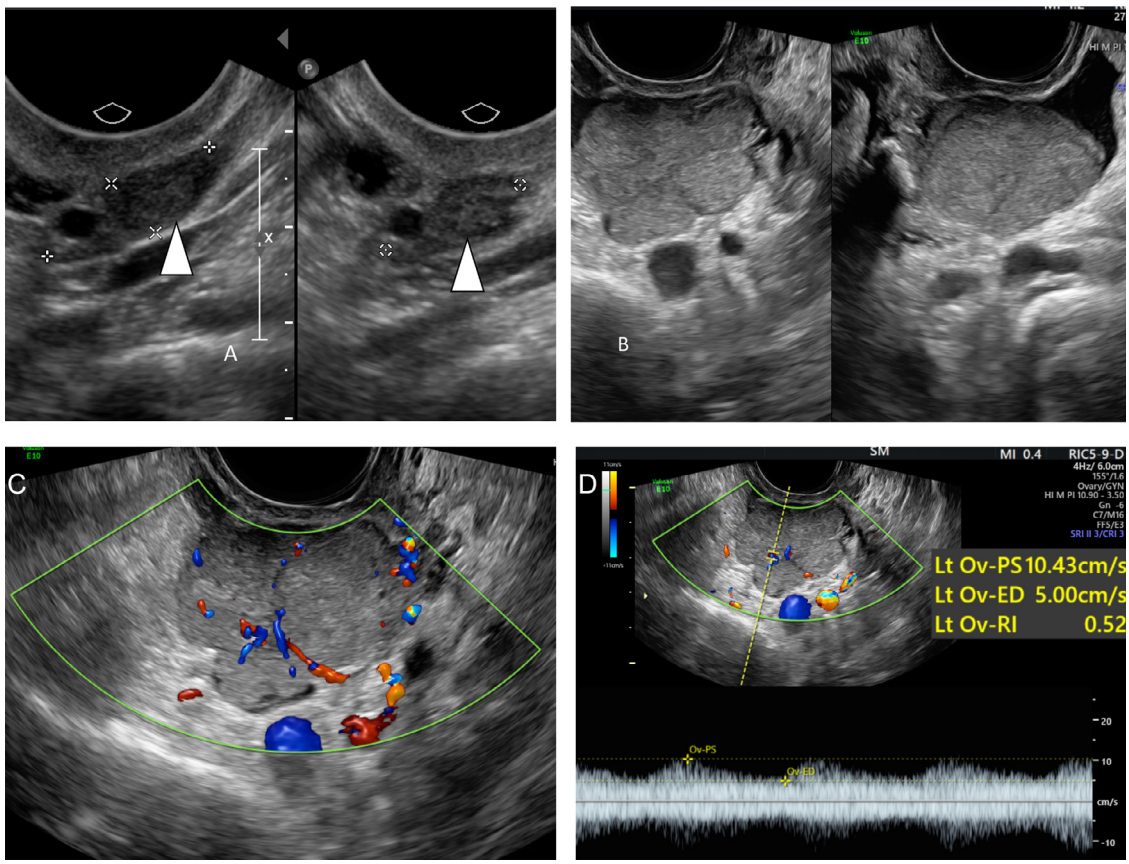

Figure 8 (A) An initial pelvic ultrasound (November 2016) shows a small 1 cm solid mass in a normal-sized ovary (arrow head). (B) A follow-up ultrasound (January 2019) shows a solid mass in the same ovary surrounded by free pelvic fluid. At surgery a malignant serous epithelial tumor was diagnosed. (C and D) Color and spectral Doppler images demonstrating moderate vascularity and a low resistance flow pattern consistent with a malignant ovarian tumor.

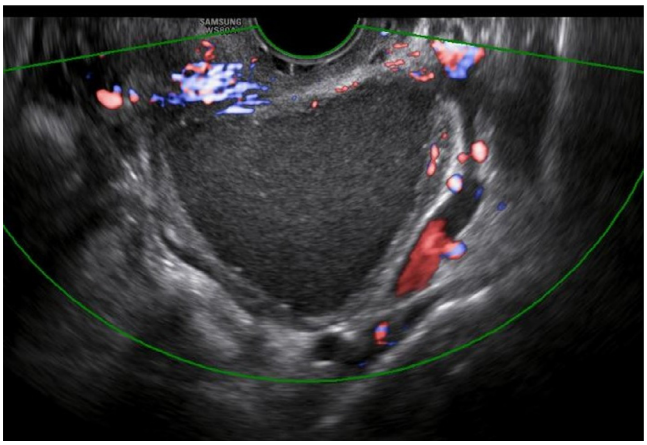

Figure 9 Color Doppler score of 1. There is no vascular flow noted within the unilocular cystic tumor proven to be an endometrioma.

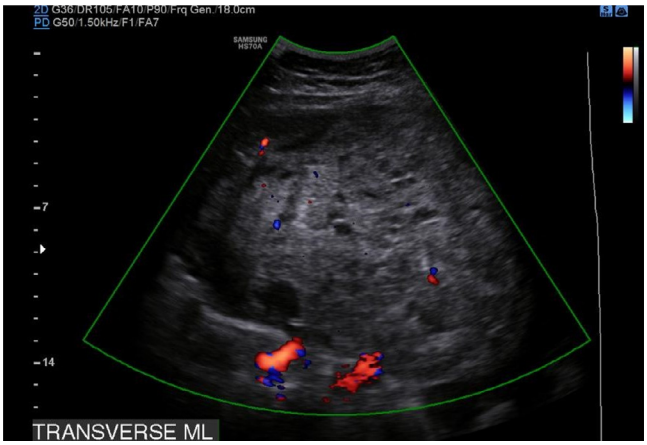

Figure 10 A predominantly solid tumor with scattered cystic changes demonstrates minimal vascular flow-color Doppler score of 2. Surgical diagnosis was a yolk sac tumor of the ovary.

48%-80% of BOTs[29-31] (Fig. 13). Presence of papillae into the cyst cavity was significantly more frequent in BOT (48%) than in benign tumors (4%) or invasive malignant tumors (4%).[29] Presence of intracystic solid tissue was similarly seen more often in invasive tumors (48%) than in BOTs (18%).[29] In a series of 27 patients, BOTs were seen in younger women and 63% of tumors exhibited intracystic papillae, in addition to diffuse internal echoes (41%), heterogenous echo pattern (26%), and multilocular septae (30%). Solid tumor was an uncommon feature in borderline ovarian tumors (15%). Increased blood flow with a low RI and PI was seen in 89% of cases.[30] Others have similarly shown BOT to show papillary projections frequently (80%) compared to benign (21%) and invasive cancers (20%). All invasive malignancies and most BOTs (80%) were vascularized on color Doppler compared to 44% of benign tumors.[31] The sonographic appearance differs with histologic types of BOT. Serous and mucinous endocervical type of BOTs are typically unilocular solid tumors with vascular papillary projections whereas the mucinous intestinal types are multilocular, with thick

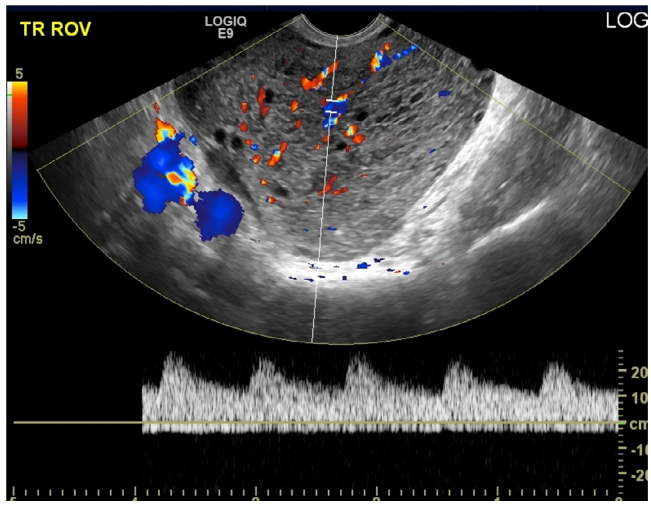

Figure 11 Predominantly solid ovarian mass with moderate vascular flow noted consistent with a color Doppler score of 3. Surgical diagnosis was an enlarged torsed polycystic ovary without a tumor.

hyperechoic septations and no solid components. This type of BOT also tends to be less vascular.[32]

Solid Ovarian Cancers

Solid tumors of the ovary form a smaller percentage (23.4%) of ovarian tumors compared to cystic tumors but account for a significant proportion of malignant (33.6%) and metastatic tumors (20%-25%) of the ovary.[7,33] Solid tumors account for only 5% of BOTs and 7% of Stage I of epithelial cancers but account for 38% of Stage II-IV epithelial ovarian cancers 56% of rare cancers and 60% of metastatic tumors to the ovary.[34] The incidence of malignancy in a solid ovarian tumor is high and tumors larger (>10 cm) have a higher malignancy rate (57%), irregular solid tumors have an even higher rate of being malignant (92%-95%).[7,33] The most common solid ovarian tumors are epithelial tumors (28.2%), germ cell tumors are next common cause (22.2%), followed by sex cord stromal tumors (21.4%) and metastatic tumors accounting for 19.7%.[33]

Malignant germ cell tumors of the ovary are rare malignant tumors of the ovary accounting for 2.6% of ovarian malignancies. These tumors arise from primitive germ cells of the embryonic gonad. A large percentage of germ cell tumors are benign, the malignancy rate of germ cell tumors is low at 5%. The most common type of a malignant germ cell tumor is a dysgerminoma (32.8%-37.5%), followed by an immature teratoma, a yolk sac tumor (endodermal sinus tumor) and mixed germ cell tumor. These tumors typically present as abdominal pain and mass in adolescence and young women. Elevated α-fetoprotein or β-hCG levels are virtually diagnostic of ovarian malignant germ cell tumors and should be measured in young women who present with a pelvic mass.[34-37] On ultrasound a dysgerminoma is typically solid, heterogeneous, with well-defined margins and is often very vascular. On MRI vascular septae are visible and the tumor is typically T1 hypointense and T2 isointense to mildly hyperintense. Yolk sac tumors formerly called as endodermal sinus tumors are more common in young women

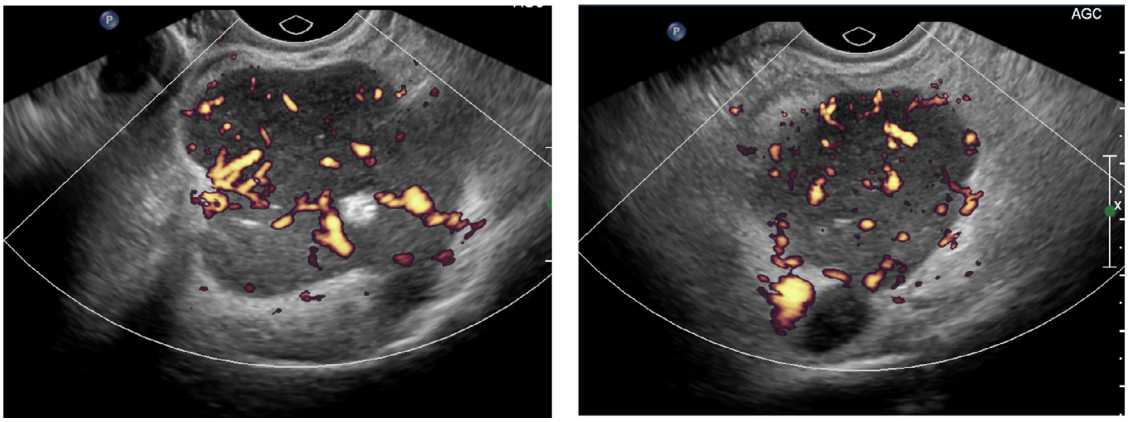

Figure 12 A large solid adnexal mass with marked vascular flow consistent with a color Doppler score of 4.

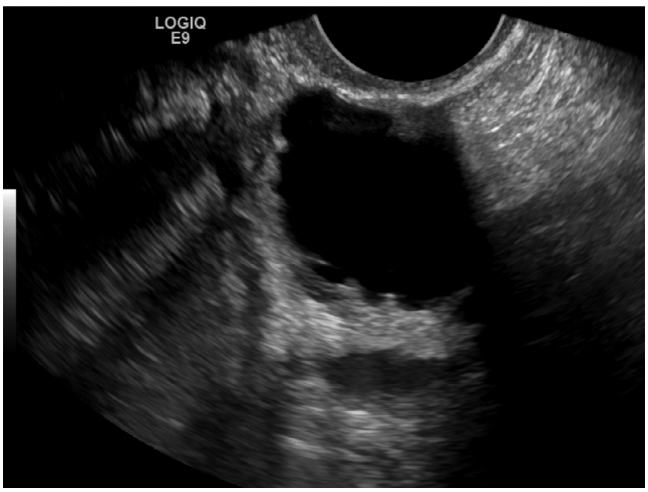

Figure 13 A unilocular cyst of the ovary with an irregular inner wall showing multiple papillary projections proven to be a Borderline ovarian tumor.

under the age of 40. On ultrasound these tumors are well defined and have solid and cystic components, the latter often septate. Foci of brightly enhancing vessels are typically described on contrast-enhanced CT and MRI, areas of hemorrhage are typical.[35] Immature teratomas appear as a heterogeneous solid mass with cystic areas and scattered calcifications, echogenic areas represent intratumoral fat and may be characteristic on CT and MRI. The malignant counterparts are distinguished from benign teratoma by presence of anechoic cyst contents and scattered small calcifications.[37]

Ovarian lymphomas are rare, frequently bilateral, median size is 8 cm, majority are secondary involvement of the ovary (90%) with the most common types being Burkitt's lymphoma (54%) followed by large cell type (31%) and mixed types (8%)[38] (Fig. 14). Metastasis to the ovaries have morphologic pattern based on the source of the primary. They tend to be typically solid, bilateral, and richly vascularized.[38] Papillary projections are rare in ovarian metastasis. Breast, gastric, and uterine cancer metastasis tend to have this typical features, metastasis from colorectal and biliary tract tends to be multilocular solid or multilocular with anechoic or low internal echoes within the cystic components. Ovarian metastasis is typically small and often associated with associated with ascites.[34]

Malignant Brenner's Tumors

Brenner's tumors are rare and constitute 1%-2% of all ovarian tumors. They are surface epithelial tumors. About 95%-99% of these tumors are benign and 1%-5% are malignant and hence overall malignant Brenner's tumors are extremely rare.[39,40] These appear as large predominantly solid tumors with amorphous calcifications and are vascular. The mean size of these tumors is 10 cm. They are typically unilateral and confined to the ovary with good prognosis and survival. In a series of 207 patients, mean age was 65 years, disease was confined to the ovary in 55.4% of cases, in whom the 5-year survival rate was 94.5%, compared to 51.3% survival for those with extraovarian spread of tumor. Distinction between benign and malignant Brenner's tumor is not possible based on imaging morphologic features.[39,40]

Cystic Ovarian Cancers

Primary invasive epithelial cancers in Stage I are morphologically similar to BOTs. Stage II-IV cancers have more solid components, more often multilocular, have a higher proportion of solid tissue. They are more commonly associated with ascites. Advanced malignant epithelial tumors of the ovary demonstrate significant vascularity with high color scores.[34] Epithelial tumors account for 85%-90% of ovarian malignancies. Epithelial tumors are generally cystic with a variable solid component. Serous cystadenocarcinomas unlike their benign counterparts tend to be multilocular with solid elements. Solid nonfatty, nonfibrous, and nonhemorrhagic tissue is a predictor of malignancy particularly when associated with ascites, peritoneal implants, organ invasion, and lymphadenopathy. Serous cystadenocarcinomas are the most common ovarian malignancy.[41] Mucinous tumors form about 10% of ovarian cancers and are less common than serous cystadenocarcinoma. Imaging features do not reliably distinguish between serous and mucinous carcinoma. They are more commonly larger and multiloculated when compared to the serous carcinoma. About 75% of serous ovarian cancers are high-grade serous carcinomas with a mean age of

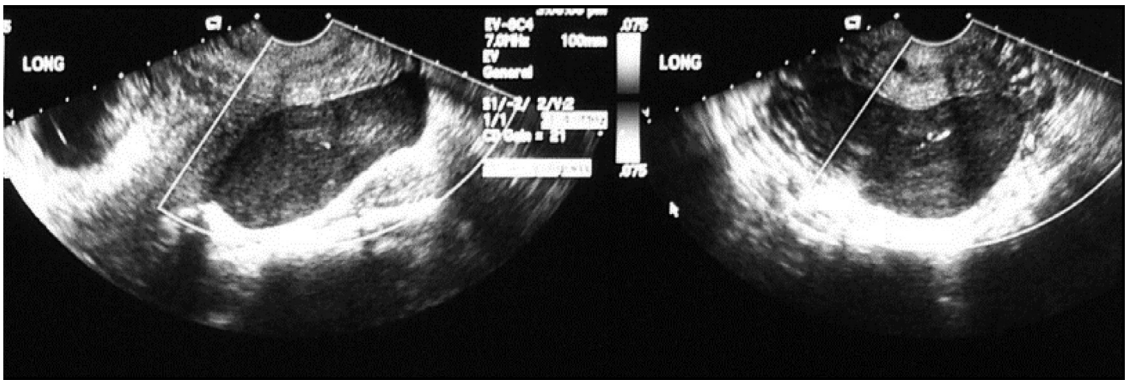

Figure 14 Ultrasound of the adnexa in a first trimester pregnancy showed bilateral solid masses with mild vascular flow. Surgical diagnosis was ovarian lymphoma.

53 years, remainder are borderline (15%) or low grade (10%) and typically present in younger women, 42-45 years, respectively. In a series of 300 high-grade invasive serous cancers, 64% of the tumors were solid, 32% were multilocular solid. Only 7% had papillary projections. Low-grade invasive serous carcinomas were not vascularized in 3.2% of cases and high grade serous carcinoma in 2.3% of cases. The mean diameter of the solid component in the low-grade invasive serous adenocarcinoma was 5 cm compared to 6.3 cm in the high-grade invasive serous adenocarcinoma.[42]

Ovarian carcinoma in a normal-sized ovary is a particular diagnostic challenge. Patients often present with metastatic disease and ascites. In a series of 409 patients with advanced high-grade serous type of epithelial tumors, 48 patients had normal-sized ovaries. These patients were older than patients with an enlarged ovary and had an overall poorer survival than those with an enlarged ovary.[43] Normal-sized ovary carcinoma syndrome term has been used for such patients with an ovarian cancer presenting with diffuse metastatic disease of the peritoneal cavity and a normal-sized ovary.[43-45]

Hormonally Active Ovarian Tumors

Hormonally active ovarian tumors arise from the gonadal ovarian stroma and are typically solid tumors (Fig. 15). In a series of 1135 women with ovarian tumors, there were 60 hormone-secreting ovarian tumors, including: 20 granulosa cell tumors, 28 fibrothecomas, 10 dysgerminomas, 2 struma ovarii, and 9 metastatic ovarian tumors. Granulosa cell tumors occurred most frequently as large unilocular-solid cysts, moderately to highly vascularized, with low-resistance vascularization. Dysgerminomas were predominantly large unilocular-solid cysts or purely solid tumors, with minimal to moderate low-resistance vascularization. Fibrothecomas were solid masses with minimal, high-resistance vascularization. Struma ovarii occurred as small, solid masses with abundant, high resistance vascularization. Metastatic ovarian tumors presented mainly as multilocular-solid tumors with strong, low-resistance vascularization. Papillary projections were most frequently observed in metastatic tumors and granulosa cell tumors in 56% and 50% of the cases, respectively, although only half of granulosa cell tumors papillary projections exceeded 3 mm. Elevated CA125 levels were found only in metastatic ovarian tumors.[46]

Doppler Interrogation of Ovarian Tumors

The penetrating and a combination of penetrating and peripheral patterns of vascularity is suggestive of adnexal malignancy. Benignity is suggested by absence of flow or regularly separated peripheral vessels. Malignant tumoral vessels are dilated

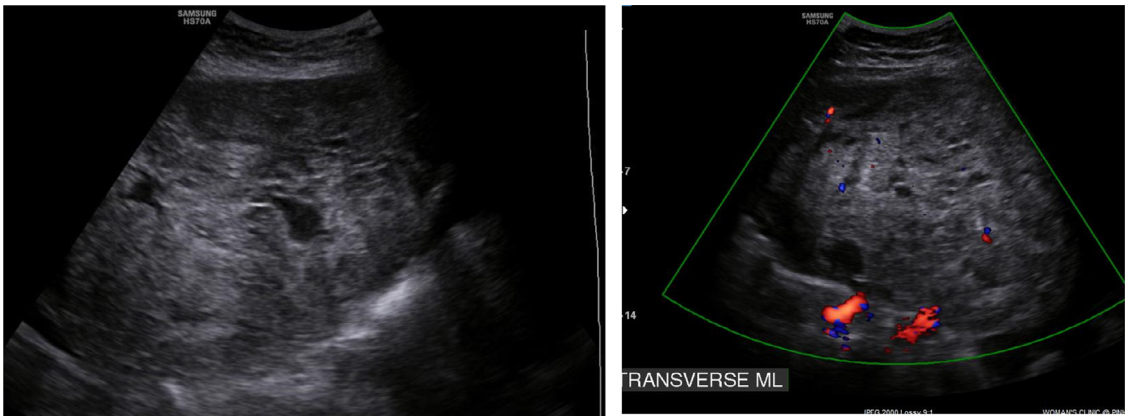

Figure 15 Hormone secreting tumor. A large solid tumor with cystic components and minimal vascular flow. Surgical diagnosis was endodermal sinus tumor.

with sacculations and tortuous. Absence of the muscular layer in these vessels leads to decreased resistance to flow that leads to a low PI and RI. Although malignant tumors typically exhibit low PI and RI, there is a considerable overlap with benign tumors and nonneoplastic adnexal abnormalities. Color Doppler ultrasound is based on mean frequency shift whereas power Doppler ultrasound is based on total integrated power of the Doppler spectrum making it more sensitive to vascular flow detection in a tumor.[47,48] Power Doppler ultrasound has been shown to be more effective in distinguishing benign from malignant ovarian tumors.[49] In a retrospective study of 43 patients suspected with Stage I cancer the detection rate was 74% using morphologic evaluation using 3D ultrasound, combined use of 3D ultrasound and 2D power Doppler ultrasound increased detection rate to 94%. Three-dimensional power Doppler imaging was not superior to 2D power Doppler ultrasound.[49] RI less than 0.4-0.8 and PI less than 1 are considered suggestive of malignancy, but reported sensitivity and specificity are widely variable due to varying threshold values and can range in sensitivity from 50% to 100% and specificity from 46% to 100%.[50]

Pathology and Staging of Ovarian Cancer

Ovarian tumors arise from 3 cell types, epithelial-stromal, sex cord-stromal, and germ cell. About 90% of ovarian cancers are malignant epithelial tumors and less than 10% are nonepithelial tumors such as malignant germ cell tumors and malignant sex cord stromal tumors. Most common malignant epithelial tumors are high-grade serous carcinoma (70%), other cell types include endometroid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%) and low-grade serous carcinoma (<5%).[51-54] Sex cord stromal tumors account for 7% of malignant tumors and include those arising from the theca cells, granulosa cells, stromal cells, and Sertoli-Leydig cells. Germ cell tumors account for 25% of benign ovarian tumors and 3%-7% of malignant tumors.[55]

The National Comprehensive Cancer Network guidelines recommend contrast-enhanced CT of the chest, abdomen, and pelvis or abdominal and pelvic MR imaging for initial work-up and surveillance of ovarian cancer. The American College of Radiology appropriateness criteria gives contrast-enhanced CT of the abdomen and pelvis the highest rating for both pretreatment staging and surveillance.[56,57] CT has limitation in identifying small peritoneal implants, with a reported sensitivity of 85%-93% and specificity of 91%-96% for tumor implants larger than 1 cm dropping to a sensitivity of 25%-50% for metastatic implants smaller than 1 cm.[55] It is now believed that majority of high-grade serous carcinomas of the ovary, primary peritoneal serous carcinomas, and primary fallopian tube carcinomas arise from the epithelium of the fallopian tube fimbriae known as the serous tubal intraepithelial carcinoma (STIC). Ovarian serous carcinomas result from STIC implants on the ovary, primary peritoneal serous carcinoma results from spillage of STIC into the peritoneum and fallopian tube carcinoma arises from STIC growing in the fallopian tube. Primary ovarian serous adenocarcinoma is distinguished from primary peritoneal serous carcinoma only by relative lack of involvement of the ovaries.[57-60] The International Federation of Gynecology and Obstetrics updated ovarian cancer staging in 2014 (Table 2).[61]

Table 2 FIGO Ovarian Cancer Staging.

Stage I: Tumor confined to 1 ovary	
I A	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
I B	Tumor involves both ovaries. Otherwise like IA.
I C	
I C 1	Surgical spill
I C 2	Capsule rupture before surgery or tumor on ovarian surface
I C 3	Malignant cells in the ascites or peritoneal washings.
STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	
II A	Extension and/or implant on uterus and/or Fallopian tubes
II B	Extension to other pelvic intraperitoneal tissues
STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
III A (Positive retroperitoneal lymph nodes and / or microscopic metastasis beyond the pelvis	
III A 1	Positive retroperitoneal lymph nodes only III A 1 (1) Metastasis < 10 mm III A 1 (2) Metastasis > 10 mm
III A 2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
III B	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
III C	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
STAGE IV: Distant metastasis excluding peritoneal metastasis	
IV A	Pleural effusion with positive cytology
IV B	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Screening for Ovarian Cancer

The World Health Organization outlines a number of important prerequisites to justify implementation of an effective screening program[62]

- Target cancer should have a high prevalence and be associated with a high mortality and morbidity.
- The screening test has to be safe, effective, and acceptable.
- The compliance of the target population in attending initial screening and diagnosis and in follow-up visits has to be high.
- Effective treatment should be available to be delivered to screen positive cases.

The low prevalence of ovarian cancer by itself does not justify screening the general population who are at an average risk. The life time risk of ovarian cancer is only 1.3%. However, the mortality rate is high with 14,080 deaths in 2017, with 60% of ovarian cancers being metastatic at the time of diagnosis conferring a survival rate of only 29%. Localized ovarian cancers on the other hand have a 5-year survival rate of 92%.[63-65] Several randomized clinical trials undertaken to test the efficacy of screening for ovarian cancer using transvaginal sonography in women with abnormal CA 125 have until recently shown no evidence of a mortality rate reduction or significant stage reduction in the intervention group compared to the control group.[63,66] Although primary analysis of the UK Colloborative Trial of Ovarian Cancer Screening data did not show a benefit, when prevalent screens were excluded a significant mortality rate reduction was observed with multimodal screening where transvaginal ultrasound was performed on women with a cut-off level of CA 125. The study included 202,638 women 50-74 years of age randomized to 3 groups: one that received multimodal screening (CA 125 and transvaginal sonography, transvaginal sonography (25% of the study group) and no screening (50% of the study group). At a median follow-up of 11.1 years, ovarian cancer was diagnosed in 0.7% of the Multimodal screening (MMS) group, 0.6% of the US group, and 0.6% of the nonscreened group. When prevalent cancers were excluded, showed a significant mortality rate reduction of 20% using a prespecified analysis of death from ovarian cancer. In the initial phase of 0-7 years of 8% and 28% from years 7-14 in favor of MMS.[67] Brown and Palmer have developed models for the growth, progression, and detection of occult serous cancers by analyzing data on serous cancer identified in Breast cancer gene (BRCA) 1 mutation carriers undergoing prophylactic bilateral salpingo-oophorectomy. They opined that ovarian cancers remain in situ, Stage I or Stage II for 4 years and 1 year as Stage III or IV before presenting clinically. Mean size of ovarian cancers for most of the occult period is 1 cm and when it progresses to Stage III or IV is only 3 cm. Based on their hypothesis, annual screening to detect ovarian cancer using transvaginal sonography may be inherently challenging.[68]

About 10% of ovarian cancers result from familial or genetic predisposition, BRCA 1, BRCA 2 mutations, and Lynch syndrome with a corresponding risk varying between 39%-65%, 11%-34%, and 3.4%-33%, respectively.[69] In women with a high risk for ovarian cancer, prophylactic bilateral salpingo-oophorectomy has been the only intervention proven to be effective in reducing mortality with a reported mortality rate reduction of 80%.[63] The largest prospective cohort study including women with a life time risk for ovarian cancer of 10% based on a family history of ovarian cancer or a genetic predisposition showed benefit from screening with transvaginal ultrasound. A sensitivity for detection of ovarian and fallopian tube cancer at 1 year was 81.3%. A PPV of 25.5% and a NPV of 99.9%. About 30.8% of screen detected cancers were Stage I or II, those that were not screened were more likely to have a stage higher than Stage III C disease.

The cost effectiveness of screening in women with an average risk of ovarian cancer has been studied. Multimodal screening (MMS) was found to be expensive and more effective in reducing ovarian cancer mortality than no screening. After accounting for uncertainty in the parameters, MMS reduced mortality by 15% with an incremental cost-effectiveness ratio ranging from $106 187 to $155 256.[70] Currently none of the North American professional societies recommend screening for ovarian cancer for women with an average risk. The Society of Gynecologic Oncology recommends screening be considered with transvaginal ultrasound and CA 125 every 6 months at ages 30-35 or 5-10 years before the age of diagnosis of youngest family member. The white paper also recommends that patients be counseled that screening has not been proven to decrease mortality and the prophylactic bilateral salpingo-oophorectomy be considered.[71]

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