

The value of contrast-enhanced ultrasonography in differential diagnosis of benign and malignant ovarian sex cord stromal tumors

Youfeng Xu¹, Nianyu Xue¹, Shengmin Zhang¹, Zhuo Wei²

¹Department of Ultrasonography, The Ningbo First Hospital, Ningbo, China; ²Ningbo University School of Medicine, Ningbo, China *Contributions:* (I) Conception and design: Y Xu, N Xue; (II) Administrative support: Y Xu, N Xue, S Zhang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: Y Xu, N Xue; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nianyu Xue. Department of Ultrasonography, The Ningbo First Hospital, 59 Liu Ting Street, Ningbo 315010, China. Email: xuenianyu010133@126.com.

Background: Sex cord-stromal tumors (SCSTs) are uncommon neoplasms that are typically difficult to diagnose before surgery due to limited experience in their medical imaging. Contrast-enhanced ultrasonography (CEUS) can evaluate the microvessel density of tumors, and the microvessel density of malignant tumors is significantly greater than that of benign tumors, so this provides a method for CEUS to differentiate benign and malignant tumors.

Methods: The CEUS diagnoses of 31 patients with pathologically confirmed SCSTs were retrospectively analyzed and compared to conventional ultrasound-based diagnoses. Based on the pathological results, the patients were divided into benign and non-benign groups. Using pathology as the gold standard, four-table data were used to evaluate the authenticity of conventional ultrasonography and CEUS.

Results: Among these 31 SCST patients, only the size of the lesion and the stripy hypoenhancement on CEUS differed significantly between the benign group and the non-benign group (P<0.05). In the benign group (n=25), 22 patients showed sparse stripes of hypoenhancement, 1 showed no enhancement, and 2 showed hyperenhancement. In 5 cases of malignant SCSTs, 4 showed hyperenhancement (with non-enhanced areas inside the tumor), and 1 showed sparse strips of hypoenhancement; in 1 case of borderline SCST, the tumor showed uniform hyperenhancement. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of the conventional ultrasound diagnoses for the 31 SCST patients were 52.0%, 16.7%, 72.2%, 7.7%, and 45.2%, respectively. In relation to CEUS, sparse strips of hypoenhancement or no enhancement were valuable diagnostic criteria for diagnosing benign SCSTs. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of CEUS were 92.0%, 83.3%, 95.8%, 71.4%, and 90.3%, respectively. The accuracy of CEUS was higher than that of conventional US, and the difference was statistically significant (χ^2 =14.467, P=0.000).

Conclusions: Sparse strips of hypoenhancement or no enhancement on CEUS are the characteristic manifestations of benign SCSTs, and hyperenhancement (with a non-enhanced area observable inside the mass) may be suggestive of malignant tumors. CEUS significantly improved the differentiation of benign and malignant SCSTs.

Keywords: Ultrasonography; microbubbles; sex cord-stromal tumor (SCST)

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Introduction

Sex cord-stromal tumors (SCSTs), which mainly include granulosa cell tumors (GCTs), fibrothecomas, and Sertoli-Leydig cell tumors, are uncommon ovarian tumors arising from stromal tissue and/or undifferentiated gonadal tissue, and account for 8% of all ovarian tumors (1-3). Most SCSTs grow slowly and have a good prognosis. Surgical resection remains the mainstay of SCST treatment; however, about 20% of SCSTs recur or metastasize (4). Unlike commonly observed ovarian epithelial tumors (5), SCSTs are typically difficult to diagnose before surgery due to limited experience of their medical imaging. The conventional ultrasonographic features of SCSTs have only been described in some case reports (6-8), and no article has separately reported on contrast-enhanced ultrasonography (CEUS) findings. CEUS can evaluate the microvessel density of tumors, and the microvessel density of malignant tumors is significantly greater than that of benign tumors. CEUS plays a great role in the differential diagnosis of benign and malignant tumors, and can significantly improve the diagnostic accuracy of conventional ultrasound. In this study, we retrospectively analyzed the CEUS manifestations of SCSTs to improve the diagnostic accuracy and reduce the misdiagnosis of SCSTs. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-301/rc).

Methods

Subjects

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Ningbo First Hospital (No. 2022RS030). Individual consent for this retrospective analysis was waived. The conventional ultrasound and CEUS data of 31 patients with pathologically confirmed SCSTs at our hospital from January 2010 to January 2022 were retrospectively analyzed. To be eligible for inclusion in the analysis, the patients had to meet the following inclusion criteria: (I) have complete conventional ultrasound and CEUS data; (II) have undergone surgery within 2 weeks of CEUS; (III) have postoperative pathologically confirmed SCSTs; and (IV) have no history of radiotherapy, chemotherapy, and/ or surgery for any tumor. The patients were aged 17–

71 years [mean \pm standard deviation (SD): 46.2 \pm 13.8 years]. The patients were divided into the benign and non-benign groups (including malignant and borderline) based on the pathological findings.

Equipment and agents

The contrast agent used in CEUS was SonoVue (Bracco SpA, Milan, Italy). The agents were microbubbles of the phospholipids microencapsulated sulfur hexafluoride (SF 6). The microbubbles had an average diameter of 2.5 µm and pH values of 4.5–7.5. After the SonoVue powder was thoroughly dissolved in 5 mL of normal saline, 2.4 mL of the solution was injected in the bolus through the cubital vein.

The ultrasound devices used included the Resona7 (Mindray Biomedical Electronics Co., Ltd., Shenzhen, China), MyLab90 (Yum Medical Equipment Co., Ltd., Shenzhen, China), LOGIQ E9 GE (General Electric Company, Boston, Massachusetts, USA), Acuson Sequoia 512 system (Siemens, Mountain View, CA, USA), EPIQ7C (Philips Electronic N.V, Amsterdam, The Netherlands), and Aplio500 (TOSHIBA CORPORATION, Tokyo, Japan). The CEUS function was available in all of these devices. A transabdominal (frequency: 2.5–4.0 MHz) or transvaginal probe (frequency: 5.0–9.0 MHz) was selected according to the conditions of each patient and mass.

Methodology

The conventional ultrasound and CEUS images of the SCSTs were retrospectively analyzed. The parameters of the conventional ultrasound images included the location, number, size, shape, echo, boundary, posterior echo, blood flow, and accompanied ascites of the tumor. The findings were interpreted by 2 physicians with 10 years of experience in obstetric and gynecological ultrasounds, and each preliminary diagnosis was made after the physicians reached an agreement. The parameters of CEUS included the enhancement time, enhancement level (high, equal, low, or none), and contrast-agent distribution (uniform or nonuniform). The findings were interpreted by 2 physicians with 5 years of experience in obstetric and gynecological ultrasounds, and each preliminary diagnosis was made after the physicians reached an agreement. All 4 physicians were blind to the final diagnoses and other imaging information at the time of the interpretation and preliminary diagnoses. The sample size of this study is small, and further studies

 Table 1 Comparison of the lesion sizes measured by ultrasound or pathology

Method	Lesion size (cm), mean \pm SD	t value	P value
Ultrasound	5.01±2.49	0.225	0.823
Pathology	5.14±2.34		

 Table 2 Comparison of CEUS parameters between the benign and non-benign SCSTs

CEUS	Benign group	Non-benign group	P value
Age (years), mean ± SD	47.08±12.83	42.50±18.17	0.474
Lesion size (cm), mean \pm SD	45.64±22.67	68.50±27.51	0.042
Echoes, n			0.237
Solid hypoechoic	17	2	
Solid isoechoic	1	1	
Solid/cystic mixed	7	3	
Posterior echoes, n			0.063
Attenuated	13	0	
Normal	12	6	
Blood flow, n			0.068
None	17	1	
Yes	8	5	
Enhancement, n			0.002
Stripy hypoenhancement	22	1	
Non-stripy hypoenhancement	3	5	

CEUS, contrast-enhanced ultrasonography; SCSTs, sex cord-stromal tumors; SD, standard deviation.

with larger samples are needed to confirm.

Statistical analysis

The statistical analysis was performed using SPSS13.0 software package (Chicago, IL, USA). Using pathology as the gold standard, four-table data were used to evaluate the authenticity of conventional ultrasonography and CEUS. The diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate were calculated. The diagnostic accuracy of conventional

ultrasound and contrast-enhanced ultrasound was compared using the χ^2 test or the Fisher exact-probability test. The measurement data are expressed as the mean \pm SD and were analyzed using a two-sample *t*-test. Two-sided P value <0.05 was considered statically significant.

Results

Clinicopathological data

Pathological findings

Among the 31 patients with pathologically confirmed SCSTs, 25 were allocated to the benign group (including 24 patients with fibrothecomas and 1 patient with a sclerosing stromal tumor), and 6 patients were allocated to the non-benign group [including 5 patients with malignant tumors (i.e., adult-type GCTs) and 1 patient with a borderline tumor (i.e., a moderately differentiated Sertoli-Leydig cell tumor)]. The lesions occurred in the left ovary in 12 patients and in the right ovary in 19 patients. In 1 patient, fibrothecomas occurred in both the left and right ovaries; in another patient, 2 fibrothecomas were found in the left ovary.

In 19 patients, the lesions were detected during routine health check-up exanimations, and in 12 patients, the lesions were detected following visits to our hospital due to symptoms, including lower abdominal distension/pain, irregular menstruation, and postmenopausal bleeding.

The tumor marker test results revealed normal tumor markers in 20 patients (among whom, 13 had benign tumors, 6 had malignant tumors, and 1 had a borderline tumor). The results also revealed slightly elevated CA15-3 (n=4), CA125 (n=3), CA19-9 (n=1) levels, squamous cell carcinoma (SCC) associated antigen (n=1), carcinoembryonic antigen (n=1) in some patients with fibrothecomas, and slightly elevated alpha-fetoprotein in 1 patient with a sclerosing stromal tumor; no other abnormal findings were detected.

Findings of conventional ultrasound and CEUS

The maximum diameters of the lesions detected by ultrasound ranged from 1.8 to 10.2 cm, and did not differ significantly from those measured by postoperative pathology testing (P>0.05; see *Table 1*). The lesions had clear boundaries and regular shapes in all 31 cases. Only 2 patients were observed to have a small amount of pelvic effusion. The ultrasound findings in the benign and non-

Gland Surgery, Vol 11, No 6 June 2022



Figure 1 Right ovarian fibrothecoma: hypoechoicity (+, measurement cursors), posterior echo attenuation, and sparse stripes of hypoenhancement (a specific feature of CEUS). (A) Gray-scale ultrasound; (B) contrast-enhanced ultrasound; (C) pathology (hematoxylineosin staining, ×10). CEUS, contrast-enhanced ultrasonography.



Figure 2 Right ovarian fibrothecoma: solid hypoechoicity with sparse stripes of hypoenhancement on CEUS. (A) Contrast-enhanced ultrasound; (B) gray-scale ultrasound; (C) pathology (hematoxylin-eosin staining, ×20). CEUS, contrast-enhanced ultrasonography.

benign groups are summarized in Table 2.

Under CEUS, no cases of thick vasa vasorum were observed. In the benign group (n=25), there were 22 cases of sparse strips of hypoenhancement [including 21 cases of fibrothecomas (see *Figures 1,2*), 1 case of a sclerosing stromal tumor (see *Figure 3*)], 1 case of no enhancement (fibrothecoma), and 2 cases of hyperenhancement (fibrothecomas) (see *Figure 4*). In the 5 cases of malignant SCSTs (all of which comprised adult-type GCTs), 4 showed hyperenhancement (see *Figure 5*), with an enhanced area inside the lesions, and 1 showed sparse strip-like hypoenhancement. In 1 case of borderline SCST (a moderately differentiated Sertoli-Leydig cell tumor), CEUS showed well-defined homogeneous solid hypoechoicity and rich blood flow (see *Figure 6*), with a few non-enhanced areas observable inside the mass, which was misdiagnosed as a malignant lesion by ultrasound.

Among the SCST patients, only the size of the lesion and the stripy enhancement on CEUS differed significantly between the benign group and non-benign group (P<0.05). With the pathological diagnosis as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of the conventional ultrasound diagnoses for the 31 SCST patients were 52.0%, 16.7%, 72.2%, 7.7%, and 45.2%, respectively. In relation to CEUS, sparse strips of hypoenhancement or no enhancement were valuable diagnostic criteria for diagnosing benign SCSTs. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of CEUS were 92.0%, 83.3%, 95.8%, 71.4%,

Xu et al. CEUS of ovarian sex cord stromal tumors



Figure 3 Right ovarian fibrothecoma: clear boundary, cystic and solid echoes, abundant blood flow, and hyperenhancement, with large necrotic areas inside the lesion. (A) Gray-scale ultrasound; (B) color Doppler flow imaging; (C) contrast-enhanced ultrasound; (D) pathology (hematoxylin-eosin staining, $\times 10$).



Figure 4 Sclerosing stromal tumor of the right ovary: solid hypoechoic mass with well-defined boundaries (+, measurement cursors). CEUS also shows sparse strips of hypoenhancement. Both the conventional ultrasound and CEUS showed similar findings for thecomas. (A) Gray-scale ultrasound; (B) contrast-enhanced ultrasound; (C) pathology (hematoxylin-eosin staining, ×10). CEUS, contrast-enhanced ultrasonography.



Figure 5 Adult-type granulosa cell tumor of the right ovary: cystic and solid echoes with a clear boundary and a characteristic multilocular honeycomb appearance on CEUS. (A) Gray-scale ultrasound; (B) contrast-enhanced ultrasound; (C) pathology (hematoxylin-eosin staining, ×20). CEUS, contrast-enhanced ultrasonography.

1090

Gland Surgery, Vol 11, No 6 June 2022



Figure 6 A moderately differentiated Sertoli-Leydig cell tumor of the right ovarian: homogeneous solid mass with clear boundary and hypoechoicity (+, measurement cursors), along with rich blood flow; CEUS showed overall high enhancement, with a few non-enhanced areas inside the lesion. (A) Gray-scale ultrasound; (B) color Doppler flow imaging; (C) contrast-enhanced ultrasound; (D) pathology (hematoxylin-eosin staining, ×10). CEUS, contrast-enhanced ultrasonography.

and 90.3%, respectively. The accuracy of CEUS was higher than that of conventional US, and the difference was statistically significant (χ^2 =14.467, P=0.000).

Discussion

Under the 2020 classification system of the World Health Organization, there are 3 types of SCSTs; that is, pure stromal tumors (e.g., fibroma, thecoma, and sclerosing stromal tumor), pure sex cord tumors (e.g., GCT and Sertoli cell tumor), and mixed SCSTs. Such tumors are basically solitary. Consistent with previous findings (9,10), in the current analysis, only 2 patients had 2 masses. Thus, a diagnosis of SCST should not be considered for patients with lesions in the bilateral ovaries or multiple lesions; however, there is a possibility that SCST may be accompanied by lesions of other origins.

SCSTs can occur at any age, but are more common in middle-aged and elderly women (9-11). In the present study, 38.7% (12/31) of the SCST patients were symptomatic (and presented with lower abdominal distention and pain, irregular menstruation, and postmenopausal bleeding), which was mainly related to the secretion of estrogen from the SCSTs. Thus, a diagnosis of SCST should be considered for patients with an adnexal mass or estrogen-related symptoms. SCSTs can secrete hormones, but many SCSTs have no clinical manifestations. In our study, >50% of the SCSTs were found incidentally on physical examination. Additionally, the tumor markers were normal in 64.5% (20/31) of the patients and were only slightly increased in the remaining cases, which suggests that tumor markers have limited clinical value. As SCSTs have no specific tumor markers, clinical diagnoses rely on ultrasonography

(ultrasound is the 1st choice for gynecological tumors). Thus, an accurate preoperative ultrasonographic diagnosis is particularly important for SCST patients.

Thecoma and fibroma are the most common SCSTs, and they can be pathologically classified into thecoma, fibrothecoma, and fibroma according to the proportion of theca cells and fibrous components. Different components have different ultrasound appearances. Notably, fibromas (and some fibrothecomas) are rich in collagen fibers and thus have the most characteristic ultrasound appearances, including hypoechoicity, posterior echo attenuation, and a lack of blood supply, and are the SCSTs most easily diagnosed by ultrasound. Among the 14 patients whose diseases were accurately diagnosed by conventional ultrasound, 9 had fibromas. The characteristics of these lesions were even more apparent on CEUS, showing sparse strip enhancement. Thecomas (including some fibrothecomas) contain more cellular components and less fibrous components. Ultrasounds generally show homogeneous echoes without posterior attenuation. These lesions can be either solid or cystic and are often misdiagnosed as fibromas or cystadenocarcinomas (12,13). However, thecomas have unique CEUS features. Subserosal myoma may appear to be perfused by the pediclefeeding artery originating from the uterine artery, and the myoma shows high enhancement as a whole. CEUS of cystadenocarcinoma shows the rapid and high enhancement of cyst wall and intracystic septum, with an uneven thickness. Conversely, thecomas have a low, concentric, and sparse stripy enhancement, which is quite different to those of myomas and cystadenocarcinomas. In the present study, 2 of the patients had thecomas, which were highly enhanced, with large necrotic areas, and were misdiagnosed as

cystadenocarcinomas. A cystadenocarcinoma is generally a mass with an unclear boundary, irregular shape, thick walls, and cystic and solid components. Papillary protrusions can be observed on the inner wall, and the blood flow is abundant in the solid components (14,15). A definite diagnosis of cystadenocarcinoma may be made on the basis of a gray-scale ultrasound morphology assessment.

Sclerosing stromal tumors are very rare and are mostly found in young women. These benign tumors have a good prognosis. Their preoperative diagnosis is difficult because of their rarity (16,17). In this study, 1 patient had a solid hypoechoic mass with well-defined borders. The lesion lacked blood supply, and CEUS also showed sparse strips of low enhancement. Both conventional ultrasound and CEUS showed similar findings for the thecoma and were unable to distinguish between these 2 lesions. However, the CEUS findings might be suggestive of a benign SCST.

A GCT is a low-grade ovarian malignant tumor that rarely metastasizes and has a good prognosis. It consists of germ cells and can be divided into adult (95%) and juvenile (5%) types (18,19). All the 5 GCT patients in the current study were adult type. The conventional ultrasound showed that the GCTs had both cystic and solid components in 3 cases and were solid in 2 cases. The GCTs might have appeared solid due to their small sizes, as hemorrhage and necrosis can easily occur in larger masses. In 2 patients, the masses had rich blood flow, which was quite different to that in the thecoma-fibroma group and similar to ovarian malignant tumors (14,15). Masses in 2 patients showed peripheral annular hyperenhancement on CEUS, and obvious internal necrosis and sparse and high enhancement (multilocular honeycomb appearance), which is more characteristic. A GCT may be considered if such a honeycomb appearance is observed. Lesions in 2 patients were obviously hyperenhanced, with necrotic areas inside, and these were misdiagnosed as cystadenocarcinomas. In 1 case, the conventional ultrasound revealed a roundlike cystic and solid mass with a clear boundary, which was considered to be a uterine fibroid. CEUS showed sparse strip-like enhancement, suggestive of a fibrothecoma. Thus, the differential diagnosis was quite difficult.

Sertoli-Leydig cell tumors can secret hormones, and can be divided into highly-, moderately-, and poorlydifferentiated tumors, corresponding to benign, borderline, and low-grade malignant tumors, respectively (20,21). In the present study, 1 case of a moderately-differentiated Sertoli-Leydig cell tumor was found to be a homogeneous solid mass with a clear boundary and hypoechoicity, along with rich blood flow; CEUS showed overall high enhancement, with a few non-enhanced areas inside the lesion, which was uncharacteristic and difficult to diagnose.

The present study had some limitations. First, as a retrospective analysis, it only analyzed the conventional ultrasound and CEUS features of SCSTs and did not investigate other imaging findings. Second, limited by the retrospective design and the difference in match models, we did not perform a CEUS-based quantitative analysis. Third, the sample size of this study is small, and further confirmation is needed in a large sample study.

In conclusion, sparse strips of low enhancement or no enhancement on CEUS are the characteristic manifestations of benign SCSTs, and high enhancement (a non-enhanced area observable inside the mass) may be suggestive of a malignant tumor. CEUS significantly improved the differentiation of benign and malignant SCSTs.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-301/rc

Data Sharing Statement: Available at https://gs.amegroups. com/article/view/10.21037/gs-22-301/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-301/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Ningbo First Hospital (No. 2022RS030). Individual consent for this retrospective analysis was waived.

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Gland Surgery, Vol 11, No 6 June 2022

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