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# Findings on conventional ultrasonography and contrast-enhanced ultrasonography in different histopathological subtypes of ovarian thecoma-fibroma group

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## Abstract

**Background** Ovarian thecoma-fibroma group (OTFG) is an unusual type of ovarian cancer with three histopathologic subtypes, but their features on ultrasonography are still poorly understood. This study evaluated the features of different histopathological subtypes of OTFG on conventional ultrasonography and contrast-enhanced ultrasonography (CEUS).

**Methods** This retrospective study enrolled sixty-nine women with pathologically confirmed OTFG who underwent preoperative CEUS. The characteristics of OTFG on conventional ultrasonography and CEUS, clinical manifestations, and laboratory findings were compared among subtypes.

**Results** Fourteen patients were diagnosed with fibroma, fifty-one with thecofibroma, and four with thecoma. Although 69% of patients were post-menopausal, thecoma patients were significantly younger than those in other two groups. Laboratory examination revealed 21.7% (15/69) of patients had high carbohydrate antigen 125 (CA-125) level. On conventional ultrasonography, 72.5% (50/69) masses showed solid type, 24.6% (17/69) showed mixed cystic-solid type, and only 2.9% (2/69) showed cystic type. On CEUS, 50% (2/4) of thecoma lesions were rapid enhancement, 58.8% (30/51) of thecofibroma lesions and 78.6% (11/14) of fibroma lesions showed slow enhancement, 75% (3/4) of thecoma lesions showed isoenhancement during the descent process, and only 13.75% (7/51) of thecofibroma lesions and 7.1% (1/14) of fibroma lesions showed isoenhancement during the descent. they varied significantly among different histopathological subtypes.

**Conclusions** The majority of OTFG is solid-like on conventional ultrasonography. Menopause is an important factor related to the subtype of OTFG. In postmenopausal patients with solid adnexal masses, slow hypoenhancement on CEUS is an important feature of fibroma. In premenopausal patients with solid or mixed cystic-solid adnexal masses, thecoma may be considered when rapid hyperenhancement, and isoenhancement or hypoenhancement during descent are observed on CEUS.

**Clinical trial number** Not applicable.

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**Keywords** Ovarian thecoma-fibroma group, Thecoma, Fibroma, Contrast-enhanced ultrasonography

## Introduction

Ovarian thecoma-fibroma groups (OTFG) are a sex cord-stromal tumor according to the 2020 World Health Organization (WHO) classification of soft tissue tumors, and accounts for 1.0–4.0% of all ovarian tumors [1, 2]. They can be diagnosed in patients of any age, but it is more common in middle-aged to postmenopausal women [3–5]. Depending on the proportion of fibroblastic stromal cells and/or luteinized theca-like cells in the tumor, OTFG can be classified into thecoma, fibrothecoma and fibroma [4, 6]. Most OTFGs grow slowly and their prognosis is good. Therefore, correct diagnosis of OTFG on ultrasonography may reduce the patients' anxiety, avoid unnecessary surgeries, and improve therapeutic strategies. However, the accurate diagnosis of OTFG is difficult before surgery. They are often misdiagnosed as uterine fibroids [7–9] or ovarian leiomyoma [5, 10], and they may even be misdiagnosed as malignant tumors when accompanied ascite and elevated cancer antigen 125 (CA125) level are present [11–14]. Several computed tomography (CT) and magnetic resonance imaging (MRI) studies have investigated the imaging characteristics of OTFG [3, 15–19]. On contrast-enhanced CT, OTFG has no or mild enhancement, while slight enhancement is present on contrast-enhanced MRI. These findings are non-specific and make their diagnosis difficult [20, 21]. CEUS can display microvascular imaging of tumors and has been proven to improve diagnostic accuracy in some diseases [22–26]. To date, no study has explored the relationship between CEUS findings and pathological subtypes of OTFG. This study aimed to retrospectively analyze the features of pathologically confirmed OTFG on conventional ultrasonography and CEUS, and the relationship between CEUS findings and pathological subtypes of OTFG was further explored. Our findings may provide evidence on the diagnosis of OTFG with CEUS to improve the diagnostic performance of CEUS in OTFG patients.

## Methods

### Clinical data

This retrospective study included 69 women with pathologically confirmed OTFG, including ovarian fibrothecoma ( $n=51$ ), fibroma ( $n=14$ ), and thecoma ( $n=4$ ). Patients were treated in the First Hospital of Ningbo University between January 2013 and December 2023. All the patients had undergone preoperative conventional ultrasonography and CEUS, and the interval between ultrasonography and surgery was no more than 3 months. The clinical information included age, menopause, vaginal bleeding, abdominal pain and CA125 level; features

on conventional ultrasonography and CEUS were also recorded. The study was approved by the Ningbo University School of Medicine Institutional Ethics Committee (2024181RS). The study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from each patient.

### Ultrasound examination

All conventional ultrasonography and CEUS were conducted using commercially available scanners: Aplio500 (TOSHIBA cooperation, Tokyo, Japan), Sequoia 512 (Siemens, Florsheim, Germany), and EPIQ7C (Philips Electronic N.V, Amsterdam, The Netherlands). A 2.5–5.0 MHz transabdominal probe and a 7.0–9.0 MHz transvaginal probe were used. The use of probes depended on the conditions of each mass; transvaginal ultrasonography was preferred when the mass and myometrium could be displayed simultaneously. CEUS was available with all the devices. Continuous multi-section scanning of the uterus, appendages and masses was conducted on conventional ultrasonography.

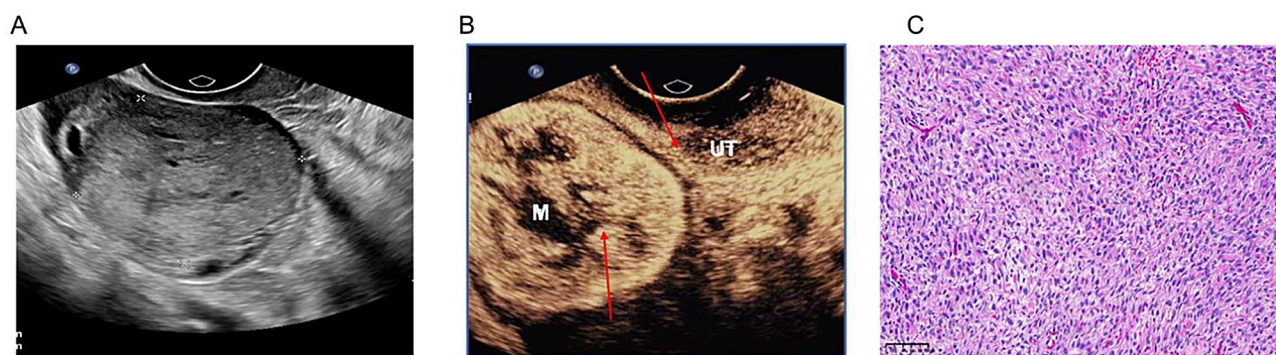
The contrast medium used for the CEUS was SonoVue (Bracco SPA, Milan, Italy), a microbubble contrast agent encapsulated sulfur hexafluoride (SF<sub>6</sub>). The probe was gently moved to find a two-dimension (2D) ultrasound imaging plane that could display the entire mass and uterus as much as possible, the CEUS mode was employed for imaging and the patient was instructed to avoid large breathing movements (hold their breath) during the imaging. Then, bolus injection of SonoVue solution (2.4 mL) was done via the median antecubital vein. Each imaging acquisition lasted at least 2 min. The contrast agent perfusion was continuously observed, and images were stored for subsequent processing and analysis.

### Imaging analysis

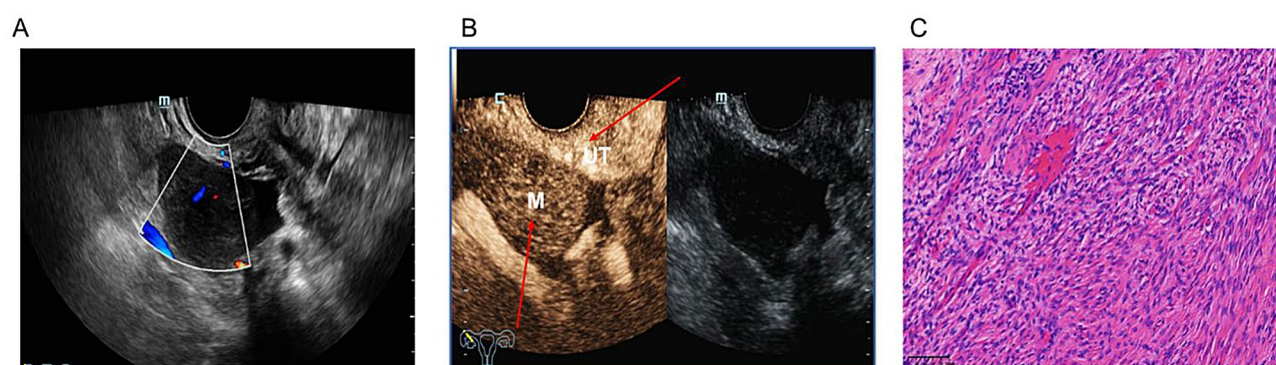
All the ultrasound images of the mass were independently analyzed by two ultrasound physicians with more than 10 years of experience in obstetric and gynecological ultrasonography. They were blind to the pathological diagnosis. Both physicians gave consistent results for each case.

The following findings on conventional ultrasonography were recorded for each tumor:

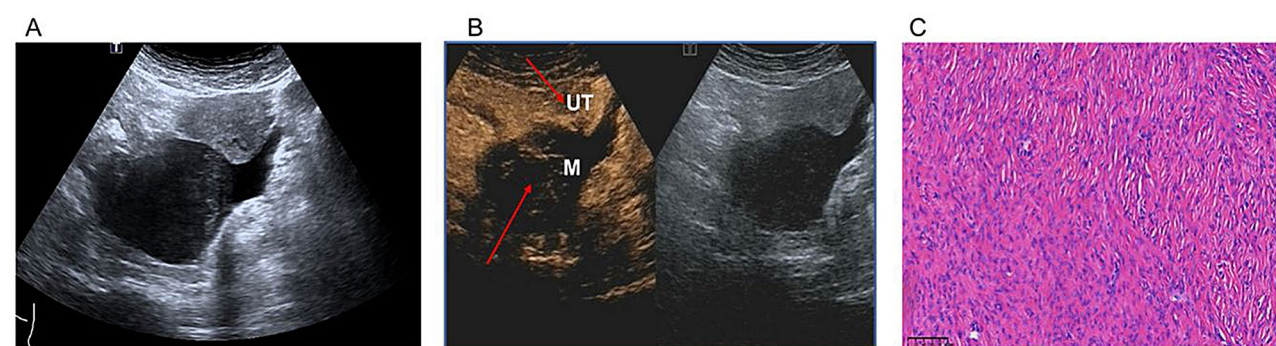
- Location: Right or left, the largest mass was described in case of bilateral lesions.
- Size: The largest diameter on ultrasonography
- Margin: Smooth, ill-defined, lobulated, or irregular



**Fig. 1** A woman with a pathologically proven thecoma. (A) Transvaginal gray-scale ultrasonography showed a 4.5 cm solid mass (+, measurement cursors). (B) Contrast-enhanced ultrasonography showed the mass (M) at the right of uterus (UT). CEUS showed hyperenhancement at the peak intensity. (C) Pathology (hematoxylin eosin,  $\times 20$ ). CEUS, contrast-enhanced ultrasonography



**Fig. 2** A woman with a pathologically proven thecofibroma. (A) Transvaginal gray-scale ultrasonography showed a 5.3 cm solid mass, and color Doppler ultrasonography revealed the color flow within the mass. (B) Contrast-enhanced ultrasound showed the mass (M) at the right of uterus (UT). CEUS showed hypoenhancement during descent. (C) Pathology (hematoxylin eosin,  $\times 20$ ). CEUS, contrast-enhanced ultrasonography



**Fig. 3** A woman with a pathologically proven fibroma. (A) Transabdominal gray-scale ultrasonography showed a 6 cm solid mass (M), at the right of uterus (UT) with posterior echo shadow. (B) CEUS showed sparse hypoenhancement (feature of CEUS). (C) Pathology (hematoxylin eosin,  $\times 20$ ). CEUS, contrast-enhanced ultrasonography

- Composition: Solid type (solid components greater than 80%), mixed cystic-solid type, or cystic type (cystic components greater than 80%) (Figs. 1A, 2A and 3A).
- Acoustic shadows: Yes or no
- Calcification foci: Yes or no

The uterine conditions were also recorded, including uterine fibroids, endometrial lesions (hyperplasia or polyps on ultrasonography), and accompanied ascites.

The parameters of CEUS analyzed included:

- Time to peak intensity: rapid, synchronous, and slow compared to the myometrium (Fig. 3B).



- Peak intensity: hyperenhancement, isoenhancement, and hypoenhancement compared to the myometrium when the enhancement peaked (Fig. 1B).
- Intensity of the lesion during descent: If the lesion intensity was lower than that of myometrium during the descent phase, it was considered hypoenhancement (Fig. 2B); otherwise, isoenhancement was considered.

### Pathological examination

The surgical tissues obtained were immediately stored in 4% formaldehyde solution and then embedded in paraffin. Then, the specimens were sectioned, and stained with hematoxylin-eosin (HE), followed by histopathological observation under a light microscope (Figs. 1C, 2C and 3C). All pathological results were obtained from the Ningbo Pathology Center.

**Table 1** Clinical and conventional ultrasound characteristics of 69 patients with OTFG

Characteristics	Thecofibroma	Fibroma	Thecoma	P
No. of lesions	51	14	4	
Age (years), median (IQR),	54 ± 11	52 ± 13	39 ± 11	
Menopausal, n				0.043
Pre-M	13	4	4	
Post-M	38	10	0	
Elevated Ca-125, n	9	5	1	0.236
Location, n				0.827
Right	27	7	3	
Left	24	7	1	
Diameter on US, n				0.566
< 5 cm	24	5	1	
5–10 cm	22	8	2	
> 10 cm	5	1	1	
Composition on US, n				0.247
Solid type	35	13	2	
Mixed cystic-solid type	14	1	2	
Cystic type	2	0	0	
Acoustic shadows, n	23	9	0	0.08
Calcifications foci on US, n	6	2	1	0.657
Endometrial hyperplasia, polyps on US, n	18	2	2	0.211
Uterine fibroid on US, n	31	4	2	0.109
Ascites, n	22	4	1	0.553

Note: OTFG = ovarian thecoma-fibroma group; No. = number; IQR = interquartile range; pre-M = premenopausal; post-M = postmenopausal; US = ultrasound; cm = centimeter; CA-125 = carbohydrate antigen 125;  $P < 0.05$  was regarded as statistically significant

### Statistical analysis

Continuous variables are presented as mean ± standard deviation ( $\bar{x} \pm SD$ ), and categorical variables as frequency or percentage. Statistical analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), and the Fisher's exact test was used to compare data among three groups. A value of  $P$  less than 0.05 was considered statistically significant.

### Results

#### Patients' characteristics

A total of 69 women with 69 masses were included in this study. The characteristics of these patients are summarized in Table 1. Of 69 masses, 53.6% (37/69) were located on the right, and 46.7% (32/69) on the left; the median age was 52.94 years (range: 21–78 years). The majority of patients (69%, 48/69) were postmenopausal. Importantly, all the pathologically confirmed thecomas occurred in the premenopausal period. Among these patients, elevation of CA125 level was observed in 15 patients (reference:  $< 35$  U/ml); 8 patients presented with emergency abdominal pain; 21 women underwent examination for irregular vaginal bleeding.

#### Findings on conventional ultrasonography

Findings on conventional ultrasonography in 69 masses are summarized in Table 1. All the masses exhibited regular shape and clear boundary. The average diameter of these masses was  $5.72 \pm 2.86$  cm (range: 1.5 to 15.3 cm), and 37 lesions had a diameter greater than 5.0 cm. The size of these lesions assessed pre-operatively was comparable to that in postoperative pathology examination ( $P > 0.05$ ).

In addition, the majority of masses (72.4%, 50/69) displayed solid type. Acoustic shadows were observed in 46.38% (32/69) of the masses, and calcification foci were present in only 9 masses. Additionally, 22 (31.88%, 22/69) patients had concomitant endometrial polyps or endometrial hyperplasia on ultrasonography, while 37 (53.62%, 37/69) patients had uterine fibroids, and 26 had ascites. There were no statistically significant differences in these findings.

#### Findings on CEUS

The findings on CEUS of 69 masses are summarized in Table 2. 58.83% (30/51) of thecofibromas and 78.57% (11/14) of fibromas showed slow enhancement, while all thecomas showed rapid or synchronous enhancement. There was statistically significant difference in the enhancement among three groups ( $P < 0.01$ ).

During the late enhancement phase, most masses (75%, 3/4) diagnosed as thecoma based on pathology exhibited equal enhancement, and statistically significant difference was observed among three groups ( $P < 0.05$ ).

**Table 2** CEUS features and pathological findings of OTFGs

Features	Thecofibroma	Fibroma	Thecoma	P
No. of lesions	51	14	4	
Time to peak, n				0.01
Rapid	2	0	2	
Synchronous	19	3	2	
Slow	30	11	0	
Peak intensity, n				0.16
Hypo-enhancement	37	11	1	
Iso-enhancement	10	3	2	
Hyper-enhancement	4	0	1	
Intensity during descent, n				0.012
Hypo-enhancement	44	13	1	
Iso-enhancement	7	1	3	

Note: No. = number; CEUS=contrast-enhanced ultrasonography;  $P<0.05$  was regarded as statistically significant

**Pathological examination**

Tumor sections were retrieved from the departmental archives of the Ningbo Pathology Center, and were reviewed for each case and confirmed by an experienced pathologist.

**Discussion**

This study included 69 cases of OTFGs, and all the tumors displayed regular shapes, predominantly round or oval. The majority (97.1%, 67/69) of masses presented as solid or mixed cystic-solid type on ultrasonography, which was consistent with previously reported [1, 6, 27, 28]. In this study, 69.6% (48/69) of lesions occurred in postmenopausal women, while all thecomas (100%, 4/4) occurred in premenopausal women. These were significantly higher than those of thecoma-fibromas (25.4%, 13/51) and fibromas (28.57%, 4/14). However, this finding was significantly different from previously reported, which suggests that OTFGs mainly occur during postmenopause [4, 29]. This discrepancy may stem from the fact that thecomas account for a low proportion of OTFGs [1], and therefore, when OTFGs were analyzed as a type of tumor, the features of thecoma may be overlooked. Despite the small sample size in this study, our finding has noteworthy clinical significance.

The contrast medium on CEUS, acting as a blood pool tracer, can reveal the distribution of blood supply in the tumor, reflecting not only the distribution of blood supply but also speed and pattern of blood flow [30–32]. Previous studies [33, 34] have demonstrated that CEUS is a valuable tool for distinguishing between malignant and benign adnexal tumors. This is also why color Doppler ultrasonography was not employed, primarily due to the its inherent limitations, such as poor red blood cell reflectivity and low signal-to-noise ratio, which reduces its sensitivity to slow blood flow and deep vessels, ultimately limiting our understanding of actual tumor blood

perfusion [22, 34]. CEUS can provide more information about the blood supply to the tumor.

Currently, no study has been conducted to comprehensively assess the findings of OTFGs on CEUS, and the criteria for classifying adnexal enhancement patterns are also unavailable [22, 35–37]. To our knowledge, our study for the first time focused on CEUS characteristics of OTFG subtypes. In the present study, findings from contrast-enhanced imaging were analyzed, drawing on analysis parameters utilized in CEUS studies of other organs. CEUS findings were collected from 69 patients in a single center over the past decade, and retrospectively analyzed in the enhancement phase, peak intensity, and late enhancement phase for the three subtypes.

Significant differences were observed in the CEUS findings among OTFG subtypes, particularly in peak enhancement time and lesion intensity during descent. All thecomas (100%, 4/4) showed rapid and synchronized enhancement, whereas only 21% (3/14) of fibromas and 41% (21/51) of thecofibromas showed rapid or synchronous enhancement. This indicates that an increase in thecoma cell proportion corresponds to a relatively abundant blood supply. During descent phase, 92% (13/14) of fibromas and 86% (44/51) of thecoma-fibromas displayed hypoenhancement, while only 25% (1/4) of thecomas showed hypoenhancement, with 75% (3/4) showing isoenhancement. These findings indicate that the characteristics of OTFG on CEUS are related to the ratio of thecoma cells to fibroblasts in the tumor. Specifically, a higher thecoma cell proportion corresponds to greater contrast agent uptake, indicating a more abundant blood supply to the tumor. All four tumors (Tumors of four subtypes) presenting rapid hyperenhancement in this study were misdiagnosed as ovarian malignancies preoperatively. Therefore, rich blood supply to the solid portion of the ovarian mass may not lead to a diagnosis of ovarian malignancy on ultrasonography, and OTFG may be suspected in case of such ultrasound findings if an elevation of Ca-125 level is not observed.

The distinct CEUS findings among different OTFG subtypes can be explained by the differences in the arteriovenous system of thecoma cells and fibroblasts within the tumor [38]. Thecoma cells have morphological characteristics similar to ovarian medulla, with spiral arteries in it; in contrast, in tissues rich in fibroblasts, there are long and straight arteries. Therefore, the spiral arterial blood supply to the tissues rich in thecoma cells can provide rich blood perfusion, which allows more contrast agent to enter the lesion, resulting in hyperenhancement of tumors rich in thecoma cells. Conversely, tumors rich in fibroblasts typically show hypoenhancement due to reduced blood supply on CEUS. The findings suggest a correlation between CEUS findings and the proportion of thecoma and fibroblasts in the tumor. Furthermore,

variations in the ratio of thecoma cells to fibroblasts may also account for the differences observed in the conventional ultrasonography.

This study has several limitations: (1) Although the use of CEUS for differentiating adnexal masses has been studied to a certain extent, there are no diagnostic criteria. The design of present study might be also influenced by subjective factors (2). The sample size was small and patients were from a single center, which might bias our results. Therefore, the interpretation of our results should be cautious (3). In the present study, different ultrasound devices and routes of examination (transabdominal or transvaginal) were used, but quantitative comparisons of CEUS parameters were not conducted.

## Conclusion

OTFGs with different pathological subtypes have different characteristics on ultrasonography. In postmenopausal women, two-dimensional solid echoes combined with low perfusion on CEUS can help the diagnosis of fibroma. In premenopausal women, an adnexal cystic-solid mass combined with rapid hyperenhancement on CEUS cannot rule out the possibility of thecoma. This study provide evidence on the diagnosis of OTFG by ultrasonography.

## Abbreviations

OTFG	Ovarian thecoma-fibroma groups
CEUS	Contrast-enhanced ultrasonography
CT	Computerized tomography
MRI	Magnetic resonance imaging
HE	Hematoxylin eosin
CA125	Cancer antigen 125

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Not applicable.

## Author contributions

Y.J.: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. Y.D.: Conceptualization, Methodology, Project administration, Validation, Visualization, Writing – review & editing. M.G.: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. Y.Y.: Data curation, Project administration, Resources, Visualization, Writing – review & editing. H.D.: Data curation, Investigation, Methodology, Project administration, Resources, Visualization, Writing – review & editing. S.Z.: Data curation, Investigation, Methodology, Project administration, Resources, Visualization, Writing – review & editing.

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## Data availability

The data supporting the current study are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ningbo University First Hospital ([2024]181RS, on September 3, 2024). The study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from each patient.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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