

Imaging in gynecological disease (17): ultrasound features of malignant ovarian yolk sac tumors (endodermal sinus tumors)

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KEYWORDS: endodermal sinus tumor; malignant germ-cell tumor; ultrasound features; yolk sac tumor

CONTRIBUTION

What are the novel findings of this work?

There are no prior published papers on transvaginal sonographic features of yolk sac tumors (YSTs). We found that malignant ovarian YSTs are mostly unilateral, large and multilocular-solid or solid, with fine-textured slightly hyperechoic solid tissue and rich vascularization.

What are the clinical implications of this work?

Sonographic features, in combination with clinical information and tumor markers, can aid in diagnosing ovarian YSTs. A correct diagnosis would make fertility-sparing surgery a potential option.

ABSTRACT

Objective To describe the clinical and sonographic characteristics of malignant ovarian yolk sac tumors (YSTs).

Methods In this retrospective multicenter study, we included 21 patients with a histological diagnosis of ovarian YST and available transvaginal ultrasound images and/or videoclips and/or a detailed ultrasound report. Ten patients identified from the International

Ovarian Tumor Analysis (IOTA) studies had undergone a standardized preoperative ultrasound examination, by an experienced ultrasound examiner, between 1999 and 2016. A further 11 patients were identified through medical files, for whom ultrasound images were retrieved from local image workstations and picture archiving and communication systems. All tumors were described using IOTA terminology. The collected ultrasound images and videoclips were used by two observers for additional characterization of the tumors.

Results All cases were pure YSTs, except for one that was a mixed tumor (80% YST and 20% embryonal carcinoma). Median age at diagnosis was 25 (interquartile range (IQR), 19.5–30.5) years. Seventy-six percent (16/21) of women had an International Federation of Gynecology and Obstetrics (FIGO) Stage I–II tumor at diagnosis. Fifty-eight percent (11/19) of women felt pain during the ultrasound examination and one presented with ovarian torsion. Median serum α -fetoprotein (S-AFP) level was 4755 (IQR, 1071–25 303) μ g/L and median serum CA 125 level was 126 (IQR, 35–227) kU/L. On ultrasound assessment, 95% (20/21) of tumors were unilateral. The median maximum tumor diameter was 157 (IQR, 107–181) mm and the largest solid component was 110 (IQR, 66–159) mm. Tumors were classified as

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either multilocular-solid (10/21; 48%) or solid (11/21; 52%). Papillary projections were found in 10% (2/21) of cases. Most (20/21; 95%) tumors were well vascularized (color score, 3–4) and none had acoustic shadowing. Malignancy was suspected in all cases, except in the patient with ovarian torsion, who presented a tumor with a color score of 1, which was classified as probably benign. Image and videoclip quality was considered as adequate in 18/21 cases. On review of the images and videoclips, we found that all tumors contained both solid components and cystic spaces, and that 89% (16/18) had irregular, still fine-textured and slightly hyperechoic solid tissue, giving them a characteristic appearance.

Conclusion Malignant ovarian YSTs are often detected at an early stage, in young women usually in the second or third decade of life, presenting with pain and markedly elevated S-AFP. On ultrasound, malignant ovarian YSTs are mostly unilateral, large and multilocular-solid or solid, with fine-textured slightly hyperechoic solid tissue and rich vascularization. © 2020 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Aim

Malignant yolk sac tumors (YSTs) are rare and there are scarce data on their morphological appearance on ultrasound examination. The aim of this study was to describe grayscale and color Doppler ultrasound features of malignant ovarian YSTs (endodermal sinus tumors), in order to facilitate their preoperative diagnosis and to determine if these tumors have a specific appearance.

Background

Epidemiology

Ovarian tumors are commonly classified as epithelial, non-epithelial or metastatic tumors from another primary malignancy. Germ-cell tumors are a subgroup within the non-epithelial group and make up about 15–20% of all ovarian tumors¹. The most common tumor among germ-cell tumors is the benign mature teratoma. Endodermal sinus tumors, more commonly called YSTs, are also germ-cell tumors, but are rare and malignant. Other germ-cell tumors are dysgerminoma, immature malignant teratoma, choriocarcinoma and embryonal carcinoma. YSTs derive from extraembryonic cell types and account for about 1% of all ovarian malignancies^{2,3}. Median age at presentation is 18–25 years³, the tumor is rarely bilateral^{4,5} and most tumors present at an early stage⁶. YSTs can occur and be treated during pregnancy^{7,8}. YSTs may also appear in the testis and in extragonadal locations⁹. Ovarian YSTs appear both

in pure form or as part of a mixed germ-cell tumor. In a recent case series, 51% (129/251) of YSTs presented in the pure form and the remainder were mixed⁶. By definition, mixed germ-cell tumors consist of two or more types of malignant germ-cell components¹⁰. The most common mixture is that of dysgerminoma and YST¹¹; other known associations are embryonal carcinoma, choriocarcinoma or immature teratoma^{9,10}. Therefore, in the pathological report, these cases should be referred to as mixed germ-cell tumor, describing the extent and percentage of all the germ-cell components observed¹².

Microscopy

Histologically, the YST is multifaceted with a diversity of features^{9,13–15}. The most characteristic histologic feature of YSTs is a reticular, glomerulus-like structure¹⁴, which caused Schiller to describe the tumors in 1939 as being of mesonephric origin¹⁶. In 1959, Teilmann¹⁶ revised this description and stated its extraembryonic germ-cell origin¹⁴. Teilmann¹⁶ named the tumors endodermal sinus tumors, because of their resemblance to endodermal sinuses in the rat placenta⁹. Later, the term YST was adopted and both terms are still commonly used^{1,9,13,14}. The resemblance of YSTs to endodermal sinuses is due to the presence of structures called Schiller–Duval bodies, that are composed of a central blood vessel lined by a layer of cuboidal or columnar cells^{1,3,16}. The Schiller–Duval bodies are cross-sections of papillary formations in a reticular labyrinth (Figure 1). When present, the Schiller–Duval bodies are diagnostic of YSTs, but they are found to be the predominant component in only 20% of cases¹⁷. When the reticular, glomerulus-like pattern merges, its interpapillary spaces can create a microcystic appearance^{9,14}. Conspicuous intracellular and extracellular hyaline droplets are present in all tumors¹. The histological diversity of YSTs can sometimes make them difficult to diagnose, as they can mimic other tumors, such as hepatoid carcinoma and clear-cell carcinoma^{9,15}. The first approach for diagnosing YSTs relies on the classical morphological parameters observed in hematoxylin and eosin stained sections (reticular, polyvesicular, glandular, hepatoid pattern, Schiller–Duval bodies, hyaline droplets)^{9,13,14,16}. Immunohistochemistry for α -fetoprotein (AFP) and glypican-3 represents a useful tool to confirm the morphological suspicion; however, the final diagnosis relies mainly on the morphological features^{14,18}.

Macroscopy

Ovarian YSTs vary in size from 5 to 50 cm³. The external surface of the tumor appears smooth and glistening with a cut surface that is tan to yellow/gray. YSTs are mostly solid tumors with cystic components, and these cystic components range in diameter from a few mm to 2 cm^{9,16,17} (Figures 2 and 3). Larger cystic degeneration is sometimes present, consisting of hemorrhage and necrosis¹.

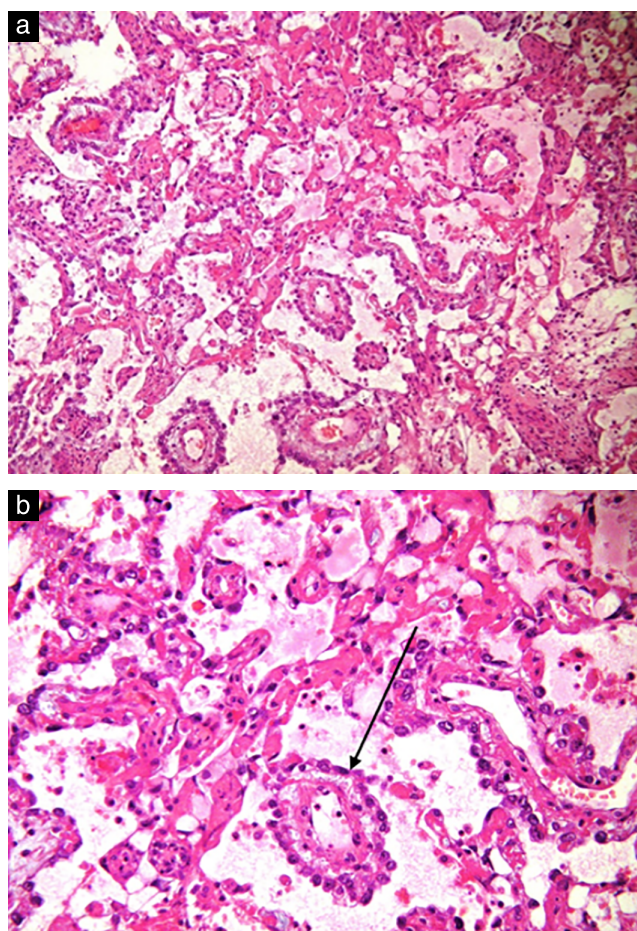


Figure 1 Histological sections of yolk sac tumor, showing overview of reticular pattern with multiple Schiller–Duval bodies (a) and close-up of Schiller–Duval body (arrow) (b).

Clinical features and prognosis

The most common symptom of an ovarian YST is abdominal pain followed by abdominal enlargement³. Duration of symptoms is often brief due to the rapid growth. About 10% of patients present with acute abdomen resulting from torsion, hemorrhage or tumor rupture¹⁹. Other symptoms may be fever, abnormal vaginal bleeding or ascites¹⁷. Serum AFP (S-AFP) is a useful marker, as elevated levels of S-AFP are present in almost 100% of cases, although elevated levels can also be present in other germ-cell tumors^{20,21}. Moreover, S-AFP levels can be used to assess treatment effects and to detect a relapse^{21–24}. Elevated serum CA 125 (S-CA 125) can also be present²⁰.

Though highly malignant, YSTs are treated effectively with a combination of surgery and chemotherapy. Before the introduction of platinum therapy, the prognosis was pessimistic, with a 3-year survival rate of 13%¹⁷. Modern treatment schedules with BEP (bleomycin, etoposide, cisplatin)⁴ improved the 5-year survival rate in women with YSTs to the current rates of 94.8%, 97.1%, 70.9% and 51.6% for International Federation of Gynecology and Obstetrics (FIGO) Stage I, II, III and IV tumors, respectively⁵. YSTs often present at an early stage and prognosis is favorable even in women with

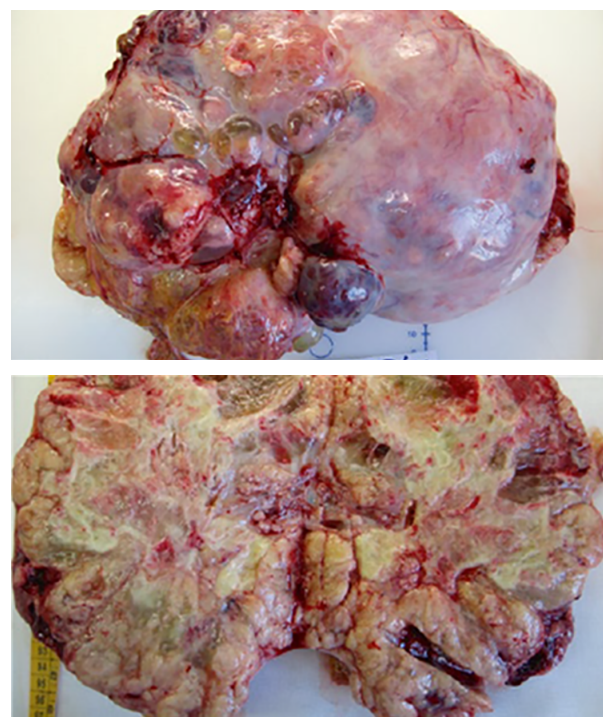


Figure 2 Gross appearance of solid ovarian yolk sac tumor.



Figure 3 Gross appearance of multilocular-solid ovarian yolk sac tumor.

metastatic disease⁶. Fertility-sparing surgery (i.e. unilateral salpingo-oophorectomy, omentectomy, peritoneal washings and biopsies) has been found to be equally as effective as radical surgery. This is also true in women with metastatic disease^{5,25,26}, partly because it is rarely a bilateral disease²⁷. Intraperitoneal seeding is the most common pattern of spread. Hematogenous spread is rare at the time of diagnosis and distant metastasis is most commonly present as malignant pleural effusion and liver metastasis²⁸.

METHODS

IOTA (International Ovarian Tumor Analysis) collaborators were invited to take part in this retrospective survey. We extracted cases with a histological diagnosis of ovarian YSTs from the IOTA database and asked centers to contribute images and additional clinical and sonographic data. We also asked the IOTA collaborators to search their patient files, local image workstations and picture archiving and communication (PAC) systems for additional cases. Inclusion criteria were preoperative transvaginal ultrasound scan with detailed documentation in the form of archived images, videoclips or a detailed ultrasound report. Ten ultrasound centers contributed 21 cases to the study: Bologna ($n=3$); Barcelona ($n=3$); Rome ($n=3$); Monza ($n=3$); Milan (National Cancer Institute; $n=1$); Bangalore ($n=2$); Cagliari ($n=1$); Leuven ($n=1$); Navarra ($n=2$); and Stockholm ($n=2$). Women from the IOTA studies had been examined between 1999 and 2016, and those investigated outside of the IOTA protocol had been examined between 2007 and 2017.

All patients had been examined preoperatively with transvaginal ultrasound (supplemented with a transabdominal scan, if necessary), using a standardized examination technique²⁹. All ultrasound examiners had more than 10 years' experience in gynecological ultrasound and the examinations were carried out using high-end ultrasound equipment. The frequency of the vaginal probes varied between 5.0 and 9.0 MHz and that of the abdominal probes varied between 3.5 and 9.0 MHz.

For women included prospectively in the IOTA studies, clinical data and ultrasound characteristics were obtained from the IOTA databases. For women who had been examined outside of the IOTA study protocol, and in cases with missing information in the IOTA database, information and ultrasound images were retrieved retrospectively from the patients' medical files and were entered into an Excel file by the principal investigator at each center. Final histology, tumor grade and FIGO stage were registered. In addition, we asked the investigators to report tumor markers (S-CA 125, S-AFP and β -human chorionic gonadotropin (β -hCG)) at the time of diagnosis, if analyzed. The masses were described using the terms and definitions published by the IOTA consortium²⁹. The presence of ascites and fluid in the pouch of Douglas was noted. The vascularization of the tumors on color Doppler was described using the IOTA color score: no detectable blood flow (1); minimal blood flow (2);

moderate blood flow (3); or abundant blood flow (4). In cases with bilateral tumors, only the largest tumor (if similar in appearance) or the tumor with the most advanced pathology was included, according to IOTA terms and definitions²⁹. The specific diagnosis suggested by the original ultrasound examiner in the IOTA database or in the original ultrasound report was recorded.

In addition to using the information collected in the IOTA database and in the patients' medical records, two examiners (E.E. and P.A.) with more than 20 and 7-years' experience in gynecological ultrasound, respectively, reassessed available ultrasound images and videoclips (most of them electronic) of YSTs with the aim to identify ultrasound patterns typical of YSTs.

Statistical analysis

Continuous data are presented as mean or median (interquartile range (IQR)) and categorical data as frequencies and percentages. Analyses were performed using Microsoft Excel 2016 or IBM SPSS v.25 (IBM Corp., Armonk, NY, USA).

RESULTS

Twenty-one patients with a histological diagnosis of ovarian YST were identified and included in this study. All cases were pure YSTs, except one (20/21), which was a mixed germ-cell tumor consisting of 80% YST and 20% embryonal carcinoma. Ten (48%) patients were previously included in the IOTA studies, while the remaining 11 were identified from local clinical and image databases. In one patient, there were no images or videoclips available and in another two cases, the images could not be re-evaluated confidently due to poor image quality, but we received clinical data and descriptive information of these tumors. Clinical characteristics are shown in Table 1. Median age was 25.0 (IQR, 19.5–30.5) years, 76% (16/21) of women were nulliparous and 76% (16/21) had a FIGO Stage I–II tumor. S-AFP level was elevated in 95% of cases and S-CA 125 level was elevated in 75% of cases. β -hCG level was measured in 11 cases and was not elevated in any. One woman had a personal history of serous borderline ovarian tumor.

An overview of ultrasound characteristics is shown in Table 2 and detailed sonographic and demographic data in each included case are shown in Table 3. Ninety-five percent (20/21) of the tumors were unilateral and one was bilateral. The median largest tumor diameter was 157 mm. All tumors were classified as either multilocular-solid (10/21; 48%) or solid (11/21; 52%) and 10% (2/21) had papillary projections. Almost all (20/21; 95%) tumors were well vascularized (color score, 3–4) (Figure 4). Only the twisted YST (Case 11 in Table 3) had no detectable blood flow, and this was also the only tumor that was classified preoperatively as probably benign. According to the ultrasound reports, 5/21 tumors were classified as probably malignant and 15/21 were classified as certainly

Table 1 Clinical characteristics of 21 patients with ovarian yolk sac tumor

Characteristic	Value
Age (years)	25.0 (19.5–30.5)
Nulliparous	16 (76)
Personal history of ovarian cancer	1 (5)
FIGO Stage	
I	14 (67)
II	2 (10)
III	4 (19)
IV	1 (5)
Serum CA 125* (normal < 35 kU/L)	126 (35–227)
Serum AFP† (normal < 8 µg/L)	4755 (1071–25 303)

Data are given as median (interquartile range) or *n* (%). *Data missing in one case. †Data missing in five cases. AFP, α -fetoprotein; FIGO, International Federation of Gynecology and Obstetrics.

Table 2 Ultrasound characteristics in 21 cases with ovarian yolk sac tumor

Characteristic	Value
Primary examination	
Pain during examination*	11/19 (58)
Largest tumor diameter (mm)	157 (107–181)
Maximum diameter of solid component (mm)	110 (66–159)
Unilateral	20 (95)
Tumor type	
Multilocular-solid	10 (48)
Solid	11 (52)
Number of locules	
≥ 10	5 (24)
5 to 9	5 (24)
0	11 (52)
Papillary projections	2 (10)
Irregular lesion	19 (90)
Echogenicity of fluid	
Anechoic	5 (24)
Low-level	6 (29)
Hemorrhagic	2 (10)
Mixed	4 (19)
No fluid	4 (19)
Color score	
1	1 (5)
2	0 (0)
3	10 (48)
4	10 (48)
Ovarian crescent sign	1 (5)
Shadowing	0 (0)
Ascites	8 (38)
Metastasis seen	3 (14)
Diagnosis suggested by ultrasound examiner	
Certainly benign	0 (0)
Probably benign	1 (5)
Uncertain	0 (0)
Probably malignant	5 (24)
Certainly malignant	15 (71)
Review of images and videoclips†	
Hyperechoic-solid tissue	
Yes	16/18 (89)
No	2/18 (11)

Data are given as *n* (%), median (interquartile range) or *n/N* (%). *Data available in 19 women. †Adequate images and/or videoclips available for 18 tumors: 17 pure yolk sac tumors and one mixed germ-cell tumor (80% yolk sac tumor, 20% embryonal carcinoma).

malignant. None of the lesions showed any acoustic shadowing. Only 38% (8/21) of cases presented with ascites.

The 18 cases with images and/or videoclips of sufficient quality available were re-assessed subjectively by two observers (P.A. and E.E.). The two observers who evaluated the grayscale and power Doppler ultrasound images in these 18 cases agreed on the following description; tumors were classified as either solid (Figures 2 and 5) or multilocular-solid (Figures 3 and 6). The majority (16/18; 89%) of tumors had inhomogeneous, but still fine-textured and slightly hyperechoic solid tissue; in solid tumors, this gave rise to a lunar-surface appearance. Ultrasound images of the two cases with papillary projections are shown in Figure 7. The two cases without hyperechoic solid tissue were multilocular-solid tumors with > 10 locules (Figure 8). The multilocular-solid tumors resembled other types of multilocular-solid tumors, for example, a granulosa-cell tumor with Swiss cheese appearance. Although the appearances of these two tumor types do overlap, there might be discrete differences as the solid tissue in granulosa-cell tumors has a coarser, slightly less echogenic, texture and more numerous and irregular locules (Figure S1).

DISCUSSION

In this study, we describe the clinical and sonographic characteristics of malignant ovarian YSTs. YSTs are often diagnosed at an early stage, in young women presenting with abdominal pain and markedly elevated S-AFP. On ultrasound, malignant ovarian YSTs present as unilateral, large, well vascularized multilocular-solid or solid lesions.

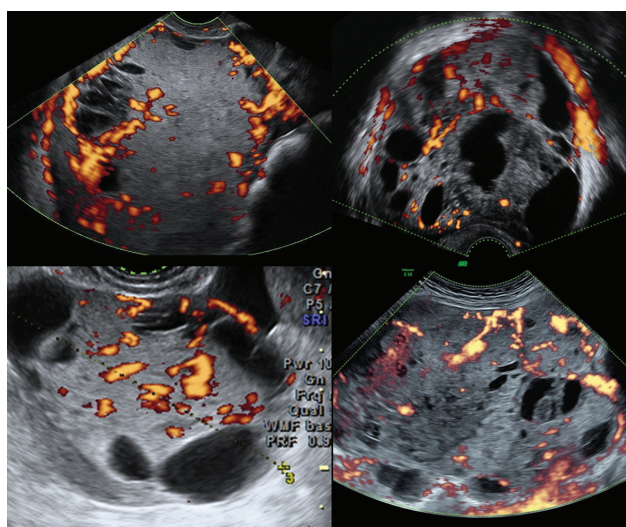
To our knowledge, this is the first study describing the transvaginal sonographic appearance of YSTs. A strength of this study is that all but one case had a pure YST, making our sonographic findings representative of this particular histological entity. Limitations are the small sample size, the retrospective study design and the lack of images of optimal quality in some cases. These facts may have limited the possibility to describe all variations and features of YSTs, also resulting in missing clinical information on S-AFP and S-CA 125 in some cases.

We have found no studies on transvaginal grayscale ultrasound features of ovarian YSTs. The study of Levitin *et al.*³⁰ from 1996 presented seven cases with an ovarian YST, assessed using transabdominal ultrasound, and described them as having ‘both echogenic and hypoechogenic components, with hypoechoic or anechoic elements predominating in four tumors’. Hung *et al.*³¹ presented a case report of an ovarian YST, describing it as ‘a large mixed cystic and solid mass with a diameter of 19 cm occupying the pelvic cavity’. Both of these descriptions match our findings. The ultrasound pattern of YSTs in this study appears to be consistent with the macroscopic gross appearance described in textbooks and reviews^{1,9,16,17}. We found one (5%) case of bilateral tumors, which matches previous findings in a larger sample showing bilateral disease in 6% of cases⁵.

Table 3 Detailed demographic and sonographic characteristics in 21 cases of ovarian yolk sac tumor

Case	Age (years)	Parity	FIGO Stage	Serum CA 125 (kU/L)	Serum AFP (μg/L)	Largest tumor diameter (mm)	Maximum diameter of solid component (mm)	Tumor type	Number of locules	Hyper-echoic solid tissue	Color score	Ascites	Presumed histological diagnosis
1	20	0	IC	64	12 200	159	159	Solid	0	Yes	4	No	Malignant rare tumor
2	19	0	IIIB	350	50	80	80	Solid	0	—†	4	Yes	Malignant rare tumor
3	40	2	IIIB	201	2	50	30	Multilocular-solid	> 10	Yes	3	Yes	Malignant rare tumor
4	25	1	IV	625	NA	20	20	Solid	0	—†	3	Yes	Borderline tumor
5	25	0	IC	62	17	170	170	Solid	0	Yes	3	No	Malignant rare tumor
6*	27	0	IB	170	NA	130	130	Solid	0	Yes	4	No	Primary ovarian cancer
7	32	0	IA	74	1071	209	209	Solid	0	Yes	3	Yes	Primary ovarian cancer
8	11	0	IA	14	5651	62	58	Solid	0	Yes	3	No	Primary ovarian cancer
9	37	0	IIIC	237	175 600	120	114	Solid	0	Yes	3	Yes	Primary ovarian cancer
10	20	0	IA	77	4755	120	74	Multilocular-solid	6	Yes	4	No	Malignant rare tumor
11	28	1	I	8	NA	110	52	Multilocular-solid	5	—‡	1	No	Benign rare tumor
12	15	0	I	18	25 303	180	98	Multilocular-solid	9	Yes	4	No	Primary ovarian cancer
13	34	0	IA	24	53 779	104	103	Multilocular-solid	> 10	Yes	4	No	Malignant rare tumor
14	21	0	IA	117	NA	157	149	Multilocular-solid	8	Yes	4	No	Malignant rare tumor
15	29	0	IIIC	196	10 874	159	159	Solid	0	Yes	4	Yes	Malignant rare tumor
16	30	3	IC	162	4346	211	119	Multilocular-solid	> 10	No	3	No	Malignant rare tumor
17	22	0	II	135	3637	109	109	Multilocular-solid	5	Yes	3	Yes	Malignant rare tumor
18	31	1	IA	26	NA	330	110	Multilocular-solid	> 10	Yes	3	No	Malignant rare tumor
19	14	0	I	NA	NA	350	350	Solid	0	Yes	3	No	Malignant rare tumor
20	26	0	IB	476	2435	181	38	Multilocular-solid	> 10	No	4	Yes	Primary ovarian cancer
21	19	0	IIIC	235	112 000	181	181	Solid	0	Yes	4	No	Malignant rare tumor

*Mixed germ-cell tumor (80% yolk sac tumor, 20% embryonal carcinoma). †Image quality inadequate for assessment. ‡No images available. AFP, α-fetoprotein; FIGO, International Federation of Gynecology and Obstetrics; NA, data not available.

**Figure 4** Typical color Doppler findings in four different ovarian yolk sac tumors.

In this series, as compared with previous studies, age (median, 25 years *vs* 18–25 years) and rate of a FIGO Stage I–II tumor (76% *vs* 38–70%) were in the upper range^{2,4,5,25,32}. One explanation for the slightly higher median age in this series could be that YSTs often present in a pediatric population and are managed by pediatricians, with transvaginal ultrasound not usually being performed, although transrectal ultrasound could

be a valuable option. The highly elevated S-AFP (median, 4755 μg/L) and S-CA 125 (median, 126 kU/L) levels in this study are in agreement with the findings of others^{3,4}. The majority of patients reported pain during examination. Pain is probably caused either by the rapid growth of the tumor leading to necrosis or by the large tumor size. Moreover, 10% of patients with malignant germ-cell tumors present with an acute abdomen resulting from torsion, hemorrhage or tumor rupture¹⁹. In this series, one case presented with clinical symptoms of torsion and was the only case classified preoperatively as probably benign, possibly because no blood flow could be detected. This highlights the fact that both Doppler and grayscale ultrasound morphology may be altered and difficult to assess in torted lesions³³.

We know that YSTs can be present together with other benign or malignant germ-cell tumors in a mixed form in around 50% of cases^{6,9,34}. In Videoclip S1, we show ultrasound imaging in a case of a germ-cell tumor including both yolk sac and benign dermoid (hyperechoic with shadowing) components. Ultrasound features of pure YSTs might not be superimposable to ultrasound features of mixed YSTs.

Although the sonographic characteristics of YSTs and granulosa-cell tumors overlap, there might be some subtle differences in the echogenicity of solid tissue (Figure S1), as the solid tissue in YSTs may appear fine-textured and slightly hyperechoic, while that of granulosa-cell tumors may appear more granulated. Still, differential diagnosis

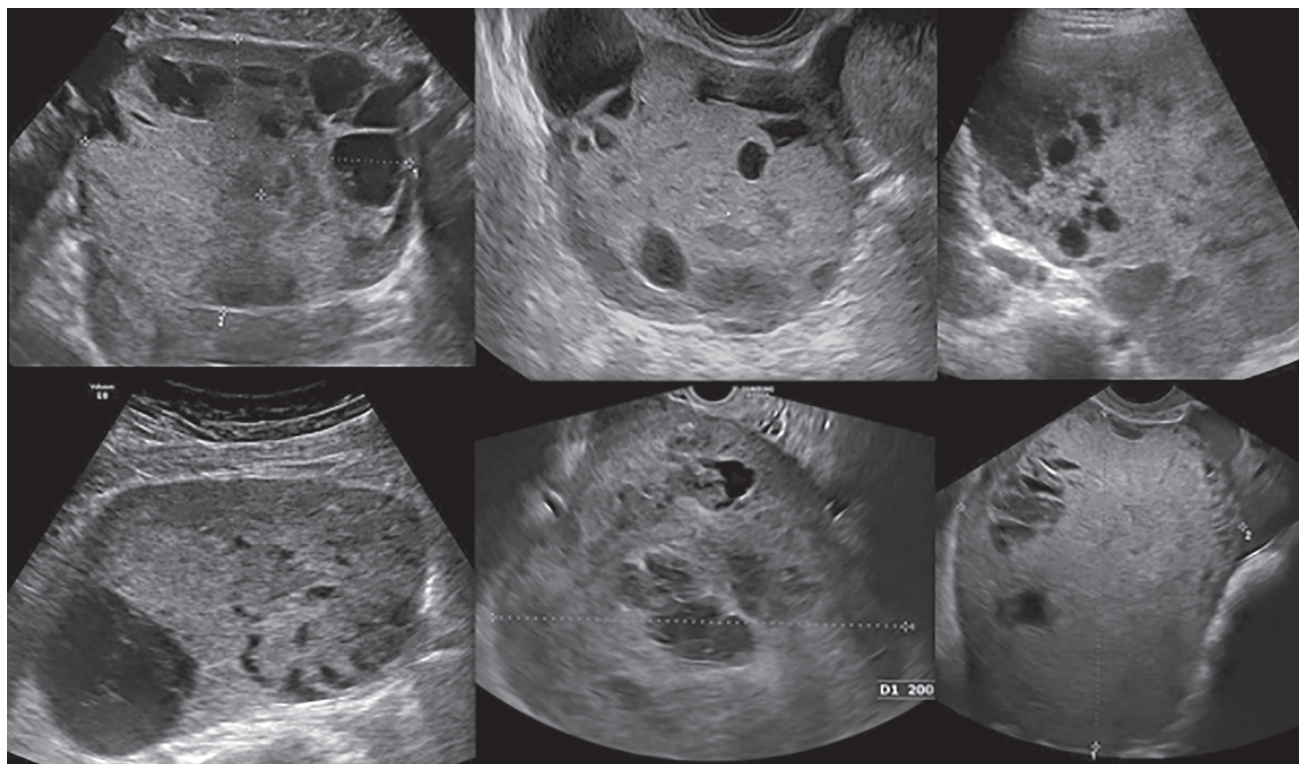


Figure 5 Ultrasound images of six different solid ovarian yolk sac tumors.

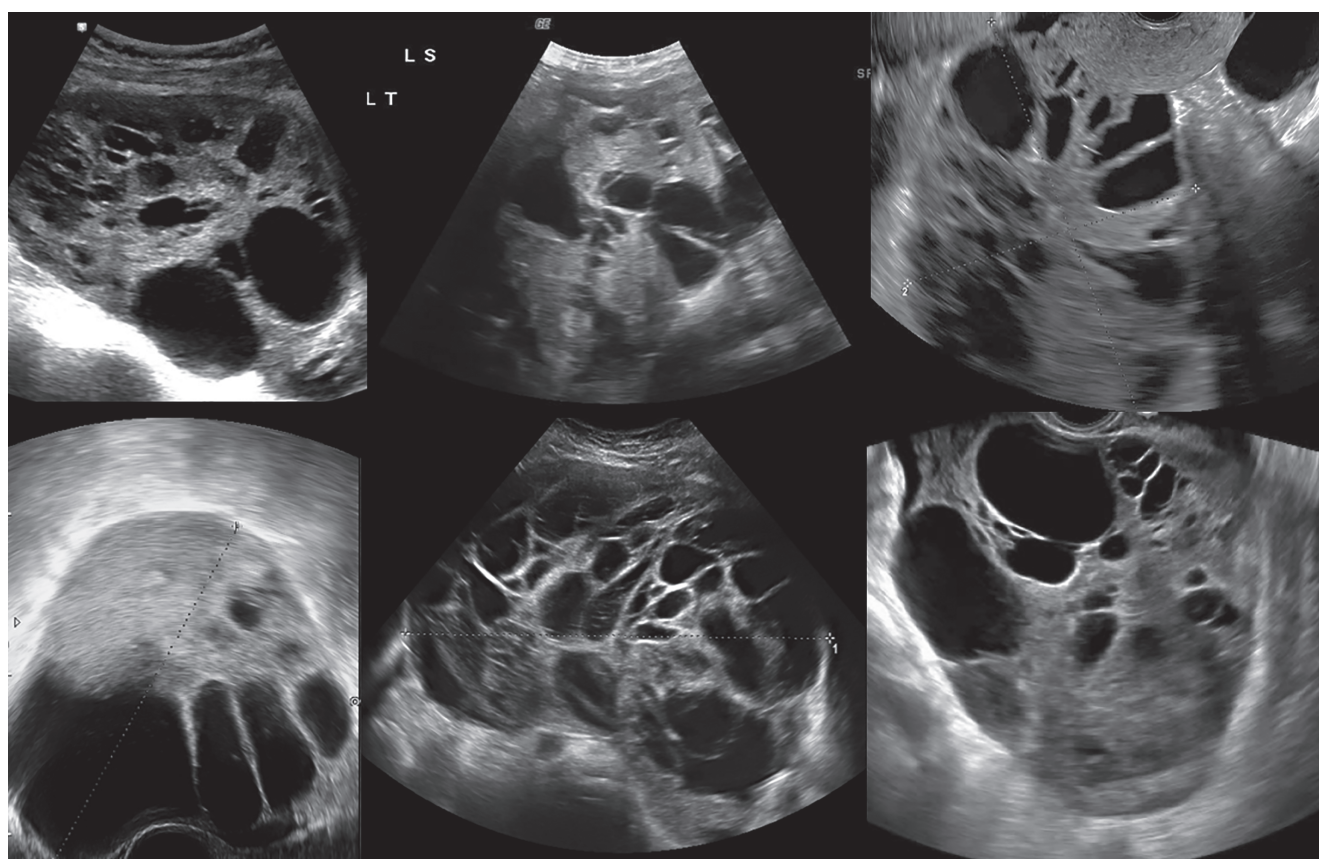


Figure 6 Ultrasound images of six different multilocular-solid ovarian yolk sac tumors.



Figure 7 Ultrasound images of two ovarian yolk sac tumors with papillary projections.

can be difficult as both tumor types can be bulky, solid or multilocular-solid, with abundant vascularization³⁵. However, combining sonographic features with clinical information (e.g. age, symptoms) and tumor markers might provide a clue to the most probable diagnosis. The sonographic appearance can guide which tumor markers should be assessed to discriminate non-epithelial from epithelial tumors, as well as providing a hint to the specific diagnosis; for example, dysgerminomas may present with elevated LDH and β -hCG³⁶, granulosa-cell tumors with elevated estrogen and inhibin³⁵, Sertoli-Leydig cell tumors with elevated testosterone or andostendione³⁷, immature teratoma with elevated AFP and CA 19-9²⁰ and YSTs with elevated AFP. We believe that increased knowledge on the sonographic appearance of rare tumors may improve clinical decision-making and patient counseling; for example, discussing the possibility of fertility-sparing surgery and the need of postoperative chemotherapy. Further collaboration through international multicenter studies, including image databases, would facilitate the growing knowledge on this topic.

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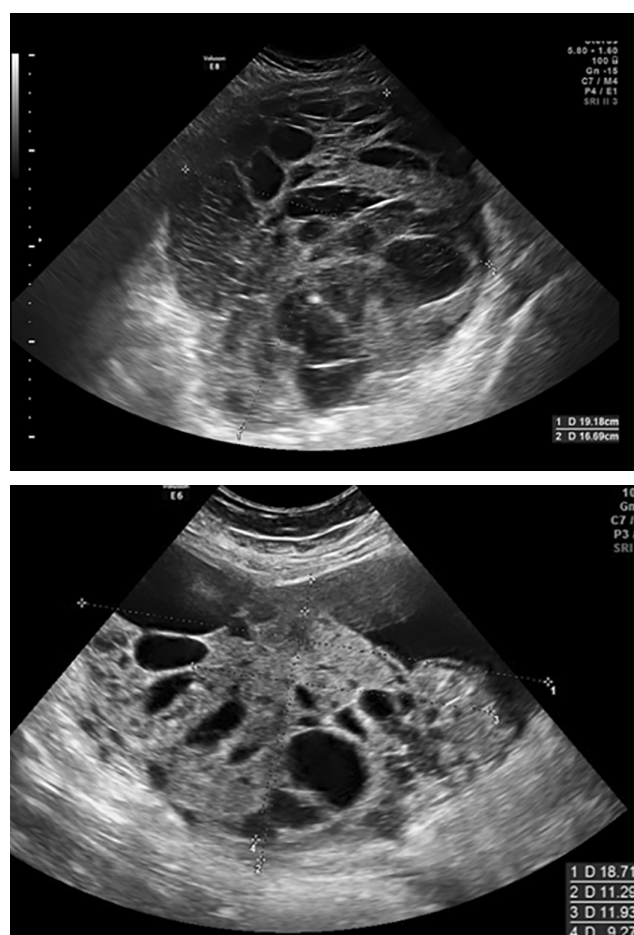


Figure 8 Ultrasound images of two ovarian yolk sac tumors without hyperechoic solid tissue.

REFERENCES

- Kumar V, Abbas AK, Aster JC, Robbins SL. *Robbins and Cotran's pathologic basis of disease* (9th edn). Saunders: Philadelphia, PA, 2015.
- Fujita M, Inoue M, Tanizawa O, Minagawa J, Yamada T, Tani T. Retrospective review of 41 patients with endodermal sinus tumor of the ovary. *Int J Gynecol Cancer* 1993; 3: 329–335.
- Dallenbach P, Bonnefoi H, Pelte MF, Vlastos G. Yolk sac tumours of the ovary: an update. *Eur J Surg Oncol* 2006; 32: 1063–1075.
- Kojimahara T, Nakahara K, Takano T, Yaegashi N, Nishiyama H, Fujimori K, Sato N, Terada Y, Tase T, Yokoyama Y, Mizunuma H, Shoji T, Sugiyama T, Kurachi H. Yolk sac tumor of the ovary: a retrospective multicenter study of 33 Japanese women by Tohoku Gynecologic Cancer Unit (TGCUC). *Tohoku J Exp Med* 2013; 230: 211–217.
- Nasioudis D, Chapman-Davis E, Frey MK, Caputo TA, Holcomb K. Management and prognosis of ovarian yolk sac tumors; an analysis of the National Cancer Data Base. *Gynecol Oncol* 2017; 147: 296–301.
- Faure Conter C, Xia C, Gershenson D, Hurteau J, Covens A, Pashankar F, Krailo M, Billmire D, Patte C, Fresneau B, Shaikh F, Stoneham S, Nicholson J, Murray M, Frazier AL. Ovarian Yolk Sac Tumors; Does Age Matter? *Int J Gynecol Cancer* 2018; 28: 77–84.
- Motegi M, Takakura S, Takano H, Tanaka T, Ochiai K. Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary. *Obstet Gynecol* 2007; 109: 537–540.
- Pafilis I, Haidopoulos D, Rodolakis A, Vlachos G, Voulgaris Z, Sotiropoulou M, Antsaklis A. Management of a pregnancy complicated by yolk sac tumor. *Arch Gynecol Obstet* 2009; 280: 803–806.
- Young RH. The yolk sac tumor: reflections on a remarkable neoplasm and two of the many intrigued by it-Gunnar Teilmann and Aleksander Talerman-and the bond it formed between them. *Int J Surg Pathol* 2014; 22: 677–687.
- Goyal LD, Kaur S, Kawatra K. Malignant mixed germ cell tumour of ovary—an unusual combination and review of literature. *J Ovarian Res* 2014; 7: 91.
- Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. *Gynecol Oncol* 1994; 55: S62–72.
- World Health Organisation. *Pathology and genetics of tumours of the breast and female genital organs*. Tavassoli FA, Devilee P (eds). IARC Press: Lyon, France, 2003.
- Ulbricht TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod Pathol* 2005; 18 Suppl 2: S61–79.

14. Nogales FF, Preda O, Nicolae A. Yolk sac tumours revisited. A review of their many faces and names. *Histopathology* 2012; **60**: 1023–1033.
15. Nogales FF, Dulcey I, Preda O. Germ cell tumors of the ovary: an update. *Arch Pathol Lab Med* 2014; **138**: 351–362.
16. Teilum G. Endodermal sinus tumors of the ovary and testis. Comparative morphogenesis of the so-called mesoepithroma ovarii (Schiller) and extraembryonic (yolk sac-allantoic) structures of the rat's placenta. *Cancer* 1959; **12**: 1092–1105.
17. Kurman RJ, Norris HJ. Endodermal sinus tumor of the ovary: a clinical and pathologic analysis of 71 cases. *Cancer* 1976; **38**: 2404–2419.
18. Zynger DL, Everton MJ, Dimov ND, Chou PM, Yang XJ. Expression of glypican 3 in ovarian and extragonadal germ cell tumors. *Am J Clin Pathol* 2008; **130**: 224–230.
19. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. *Cancer Treat Rev* 2008; **34**: 427–441.
20. Kawai M, Kano T, Kikkawa F, Morikawa Y, Oguchi H, Nakashima N, Ishizuka T, Kuzuya K, Ohta M, Arii Y, Tomoda Y. Seven tumor markers in benign and malignant germ cell tumors of the ovary. *Gynecol Oncol* 1992; **45**: 248–253.
21. Talerma A, Haije WG, Baggerman L. Serum alpha-fetoprotein (AFP) in diagnosis and management of endodermal sinus (yolk sac) tumor and mixed germ cell tumor of the ovary. *Cancer* 1978; **41**: 272–278.
22. Ishiguro T, Yoshida Y, Tenzaki T, Ohshima M, Suzuki H. AFP in yolk sac tumor and solid teratoma of the ovary: significance of postoperative serum AFP. *Cancer* 1981; **48**: 2480–2484.
23. Sell A, Sogaard H, Norgaard-Pedersen B. Serum alpha-fetoprotein as a marker for the effect of post-operative radiation therapy and/or chemotherapy in eight cases of ovarian endodermal sinus tumour. *Int J Cancer* 1976; **18**: 574–580.
24. Davidoff AM, Hebra A, Bunin N, Shochat SJ, Schnauffer L. Endodermal sinus tumor in children. *J Pediatr Surg* 1996; **31**: 1075–1078.
25. Cicin I, Saip P, Guney N, Eralp Y, Ayan I, Kebudi R, Topuz E. Yolk sac tumours of the ovary: evaluation of clinicopathological features and prognostic factors. *Eur J Obstet Gynecol Reprod Biol* 2009; **146**: 210–214.
26. Nawa A, Obata N, Kikkawa F, Kawai M, Nagasaka T, Goto S, Nishimori K, Nakashima N. Prognostic factors of patients with yolk sac tumors of the ovary. *Am J Obstet Gynecol* 2001; **184**: 1182–1188.
27. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. *Best Pract Res Clin Obstet Gynaecol* 2012; **26**: 347–355.
28. Woodward PJ, Hosseinzadeh K, Saenger JS. From the archives of the AFIP: radiologic staging of ovarian carcinoma with pathologic correlation. *Radiographics* 2004; **24**: 225–246.
29. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I, International Ovarian Tumor Analysis G. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. *Ultrasound Obstet Gynecol* 2000; **16**: 500–505.
30. Levitin A, Haller KD, Cohen HL, Zinn DL, O'Connor MT. Endodermal sinus tumor of the ovary: imaging evaluation. *AJR Am J Roentgenol* 1996; **167**: 791–793.
31. Hung JH, Shen SH, Hung J, Lai CR. Ultrasound and magnetic resonance images of endodermal sinus tumor. *J Chin Med Assoc* 2007; **70**: 514–518.
32. Nasioudis D, Chapman-Davis E, Frey MK, Caputo TA, Holcomb K. Management and prognosis of ovarian yolk sac tumors: an analysis of the National Cancer Data Base. *Gynecol Oncol*; **147**: 296–301.
33. Lourenco AP, Swenson D, Tubbs RJ, Lazarus E. Ovarian and tubal torsion: imaging findings on US, CT, and MRI. *Emerg Radiol* 2014; **21**: 179–187.
34. Gershenson DM, Del Junco G, Copeland LJ, Rutledge FN. Mixed germ cell tumors of the ovary. *Obstet Gynecol* 1984; **64**: 200–206.
35. Van Holsbeke C, Domali E, Holland TK, Achten R, Testa AC, Valentin L, Jurkovic D, Moerman P, Timmerman D. Imaging of gynecological disease (3): clinical and ultrasound characteristics of granulosa cell tumors of the ovary. *Ultrasound Obstet Gynecol* 2008; **31**: 450–456.
36. Guerriero S, Testa AC, Timmerman D, Van Holsbeke C, Ajossa S, Fischerova D, Franchi D, Leone FP, Domali E, Alcazar JL, Parodo G, Mascilini F, Virgilio B, Demidov VN, Lipatenkova J, Valentin L. Imaging of gynecological disease (6): clinical and ultrasound characteristics of ovarian dysgerminoma. *Ultrasound Obstet Gynecol*; **37**: 596–602.
37. Demidov VN, Lipatenkova J, Vikhareva O, Van Holsbeke C, Timmerman D, Valentin L. Imaging of gynecological disease (2): clinical and ultrasound characteristics of Sertoli cell tumors, Sertoli–Leydig cell tumors and Leydig cell tumors. *Ultrasound Obstet Gynecol* 2008; **31**: 85–91.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Figure S1 Comparison of sonographic features between ovarian yolk sac tumors and adult granulosa-cell tumors.



Videoclip S1 Ultrasound imaging of mixed germ-cell tumor with both yolk sac tumor and benign dermoid components. Dermoid component is seen as hyperechoic components with shadowing.