Ultrasound Obstet Gynecol 2013; **41**: 452–458
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12276

Imaging in gynecological disease (8): ultrasound characteristics of recurrent borderline ovarian tumors

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KEYWORDS: borderline ovarian tumors; ovary; recurrence; ultrasonography

ABSTRACT

Objectives *To describe the sonographic characteristics of borderline ovarian tumor (BOT) recurrence.*

Methods *From the databases of five ultrasound centers, we retrospectively identified 68 patients with histological diagnosis of recurrent BOT who had undergone preoperative ultrasound examination. All recurrences were detected during planned follow-up ultrasound examinations. Recurrent lesions were described using the terms and definitions of the International Ovarian Tumor Analysis (IOTA) group.*

Results *Sixty-two patients had a serous BOT recurrence and six a mucinous BOT recurrence. All patients except one were premenopausal, 84% of them being < 40 years old. All but one patient were asymptomatic at diagnosis of the recurrence. Fertility-sparing surgery of the recurrent tumor was performed in 57/68 (84%) patients. The most frequent ultrasound feature of recurrent serous BOT was a unilocular solid cyst (49/62, 79%) and almost half of the recurrent serous BOTs (29/62, 47%) had multiple papillary projections. In 89% of the recurrent serous BOTs there was at least one papillation with irregular surface and in 73% there was at least one papillation vascularized at color Doppler examination. Recurrent mucinous BOTs appeared mainly as multilocular or multilocular solid cysts (5/6, 83%).*

Conclusion *Sonographic features of recurrent BOT resemble those described by others for different subtypes of primary BOT.* *Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Aim

To describe the sonographic characteristics of recurrent borderline ovarian tumor (BOT) after conservative surgery for a primary or recurrent tumor.

Background

Epidemiology

Tumors of low malignant potential (BOTs) account for 15% of all epithelial ovarian cancers. They seem to arise from cortical inclusion cysts of the ovarian epithelial surface after cyclic ovulation-induced rupture and aging with acquisition of a Müllerian epithelial phenotype through metaplasia[1–3]. This metaplastic tissue is exposed to hormonal and inflammatory stimuli that can induce dysplastic transformation into BOT. Subsequently, replicative stress and DNA damage can lead to mutations and transformations into endometrioid, mucinous and low-grade serous carcinoma[3–6]. This pathway seems to be different from that leading to high-grade serous carcinomas, which more likely emerge from cancer cells in the Fallopian tube shed on the ovarian surface[7,8]. The incidence of BOTs is estimated to be 4.8/100 000 women per year[9]. Median age at diagnosis is at least 10 years less than that for invasive ovarian cancers, and almost 30% of patients are younger than 40 years[10]. The reported recurrence rate after fertility-sparing surgery varies between 15% and 35% depending on the type of conservative surgery. Recurrence may be observed several

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Accepted: 12 July 2012

years after conservative as well as radical surgery for a BOT[10–12]. Recurrence is most often seen in residual ovaries after conservative surgery but may also occur as invasive or non-invasive peritoneal implants after both conservative and radical surgery where the uterus and ovaries have been removed[13].

Microscopy

Recurrent BOTs have the same microscopic features as the primary BOT. Serous BOTs are characterized by the presence of extensive epithelial stratification, detachment of cell clusters and hierarchical branching with smaller papillae emanating from larger, more centrally located papillae. Nuclei are basally located and tend to be ovoid or rounded. Mitoses are not common and rarely exceed four per 10 high-power fields. Because of their complex papillary patterns, BOTs often display stromal invagination but not 'destructive' stromal invasion[14]. The presence of micropapillary/cribriform patterns is associated with a higher recurrence rate[12]. Mucinous BOTs are characterized by glands and cysts lined by epithelial cells, some or all of which contain abundant intracytoplasmic mucin. The neoplastic cells may resemble those of the endocervix or intestine. The architecture of endocervical-like mucinous BOTs is similar to that of serous BOTs with both large, bulbous papillae and smaller papillae with prominent cellular budding. The papillae are lined with slightly or moderately atypical cells. Intestinal-type mucinous BOTs either lack papillae or have branching filiform papillae. The cysts and papillae in mucinous BOTs of the intestinal type are lined with atypical epithelium that contains variable numbers of goblet cells and other intestinal cell types[14].

Macroscopy

Serous BOTs are composed of thin-walled cysts filled with watery fluid with polypoid excrescences accompanied by finer papillae that occupy part or all of the cyst lining, the outer surface of the ovary or both[14]. Mucinous intestinal-type BOTs tend to be the largest of all BOTs. They are almost always cystic with many cyst locules. Typically, these have thin walls and contain thick to watery mucinous fluid. Endocervical-like BOTs are smaller and contain fewer locules than those lined with intestinal type epithelium. They often contain papillae or solid areas, which may be soft and mucoid[14].

Clinical symptoms

Recurrent BOTs are usually detected on scheduled follow-up scans in asymptomatic women.

Prognosis

Recurrent BOTs have an excellent prognosis[13]. Although the rate of relapse is higher in patients who have undergone fertility-sparing surgery than in those who have undergone radical surgery, conservative surgery for BOTs does not impact on patient survival[13,15–18]. The prognosis remains good even when non-invasive implants are present, and a conservative surgical approach to recurrence can be considered also in patients with such implants[19]. Therefore, conservative surgery in cases of BOT can be proposed safely to young patients wishing to preserve their fertility potential. The reported spontaneous pregnancy rate after conservative surgery in a BOT varies between 32% and 65%[20–22], and in cases of infertility, ovulation induction or *in vitro* fertilization has been performed[22,23]. However, progression from BOT to low-grade serous carcinoma has been described[11], and exceptional deaths due to both serous and mucinous BOTs have been reported after fertility-sparing surgery[17,18,24,25].

METHODS

From the databases of five ultrasound centers (European Institute of Oncology, Milan, Italy; Policlinico Gemelli, Catholic University of Sacred Heart, Rome, Italy; San Gerardo Hospital, University of Milan Bicocca, Monza, Italy; General Faculty Hospital, Oncogynecological Center, Charles University Prague, Czech Republic; Ospedale San Giovanni di Dio, University of Cagliari, Cagliari, Italy) 68 patients with histological diagnosis of recurrent BOT were identified. All recurrences were detected during planned follow-up ultrasound examinations. These were performed every 3 months for the first 2 years following surgery and every 6 months thereafter. The 68 patients underwent preoperative ultrasound examination by an experienced ultrasound examiner between 2003 and 2010; 46 patients were from Milan, 10 from Monza, eight from Rome, two from Prague and two from Cagliari. Thirteen (19%) patients were examined within the framework of scientific studies (International Ovarian Tumor Analysis; IOTA) using a standardized examination technique and following a strict research protocol. Of the remaining 55 patients, 47 were examined following a fixed clinical examination protocol. All patients were examined with transvaginal ultrasound supplemented with transabdominal scan if necessary. All ultrasound examinations were carried out using high-end ultrasound equipment, the frequency of the vaginal probes varying between 5.0 and 9.0 MHz and that of the abdominal probes between 3.5 and 5.0 MHz.

Ultrasound images, ultrasound reports, research protocols (when applicable) and patient records were retrieved. One author from each center retrospectively characterized the tumor from his/her own center on the basis of ultrasound images, ultrasound reports and research protocols using the terms and definitions published by the IOTA group[26]. The diagnosis suggested by the original ultrasound examiner in the original ultrasound report was also noted. Results of Doppler examinations are reported in terms of presence of flow within papillary projections and color score[26]. In cases of multiple lesions suspected to be recurrences, the largest lesion was included in the

Table 1 Clinical characteristics of 68 patients with recurrent borderline ovarian tumor (BOT) after conservative surgery

	SBOT (n = 62)	*Endocervical type MBOT (n = 2)*	*Intestinal type MBOT (n = 4)*	*All (n = 68)*
Primary BOT				
Surgery of the primary BOT				
Unilateral cystectomy	14 (22)	2 (100)	0	16 (24)
Bilateral cystectomy	22 (35)	0	0	22 (32)
Unilateral oophorectomy	19 (31)	0	4 (100)	23 (34)
Unilateral oophorectomy and contralateral cystectomy	7 (11)	0	0	7 (10)
FIGO stage				
I	25 (40)	1 (50)	4 (100)	30 (44)
II/III without invasive implants	27 (44)	1 (50)	0	28 (41)
II/III with invasive implants	8 (13)	0	0	8 (12)
Not available	2 (3)	0	0	2 (3)
Recurrent BOT				
Months from primary diagnosis to diagnosis of recurrent tumor	34.5 (4–151)	24.5 (13–36)	27 (6–154)	33 (4–154)
Recurrence				
First	42 (68)	1 (50)	3 (75)	46 (68)
Second	17 (27)	1 (50)	1 (25)	19 (28)
Third	3 (5)	0	0	3 (4)
Extraovarian implants at surgery				
Invasive	3 (5)	0	0	3 (4)
Non-invasive	17 (27)	0	0	17 (25)
Age at diagnosis (years)	31 (16–53)	34 (32–36)	39 (32–40)	32 (16–53)
CA 125 at diagnosis* (U/mL)	20 (4–322)	22.5 (20–25)	13 (7–19)	20 (4–322)
Surgical treatment				
Conservative				
Unilateral cystectomy	37 (60)	2 (100)	3 (75)	42 (62)
Bilateral cystectomy	9 (15)	0	0	9 (13)
Unilateral oophorectomy	6 (10)	0	0	6 (9)
Unilateral oophorectomy and contralateral cystectomy	0	0	0	0
Non-conservative	10 (16)	0	1 (25)	11 (16)

Results are given as median (range) or *n* (%). *CA 125 was available in 65 cases. SBOT, serous borderline ovarian tumor; MBOT, mucinous ovarian borderline tumor.

statistical analysis. Clinical information was retrieved retrospectively from patient records. All clinical and ultrasound information was entered into an Excel file, which was used for statistical analysis (Microsoft Office Excel 2003, Redmond, WA, USA).

RESULTS

Sixty-two patients had a recurrence of serous BOT and six patients had a recurrence of mucinous BOT (two of endocervical type and four of intestinal type). Forty-six patients (68%) were diagnosed at first recurrence; 19 patients had experienced one previous recurrence and three patients had experienced two previous recurrences.

Clinical characteristics of the patients are shown in Table 1. All patients except one were premenopausal, and 57 (84%) were younger than 40 years. In 36 (53%) patients the FIGO stage at diagnosis of the primary tumor was higher than Stage I, with invasive implants in eight (12%) cases. Conservative surgery at diagnosis of the primary BOT preserved both ovaries in 38 (56%) patients. Results of serum CA 125 measurements at recurrence were available for 65 patients, 48 (74%) having values < 35 U/mL. Only one patient complained of symptoms (pelvic pain and bloating) at diagnosis of the recurrence.

At surgical exploration all 68 patients with recurrent BOTs were found to have optimally resectable disease. Conservative surgery was performed in 57 (84%) patients. In the remaining 11 patients, the patient's age (in five cases) or the presence of only minimal normal ovarian parenchyma, as judged by the surgeon after previous conservative surgery (in six cases), resulted in a decision to remove the entire ovary harboring the recurrence. Twenty (29%) patients were diagnosed with extraovarian implants associated with the recurrence, three of whom had histologically confirmed invasive implants and 17 of whom had histologically confirmed non-invasive implants. These implants were not detected at transvaginal ultrasound examination and all measured < 3 mm at surgical and pathological examination. At ultrasound examination of the recurrences included in this study, bilateral ovarian lesions were detected in 10 (26%) of the 38 patients with two ovaries, and multiple (up to six) separate lesions within the same ovary were observed in 19 (28%) patients (Figure 1). Sonographic characteristics of the BOT recurrences according to histological type are presented in Table 2. Thirteen (19%) recurrent BOTs

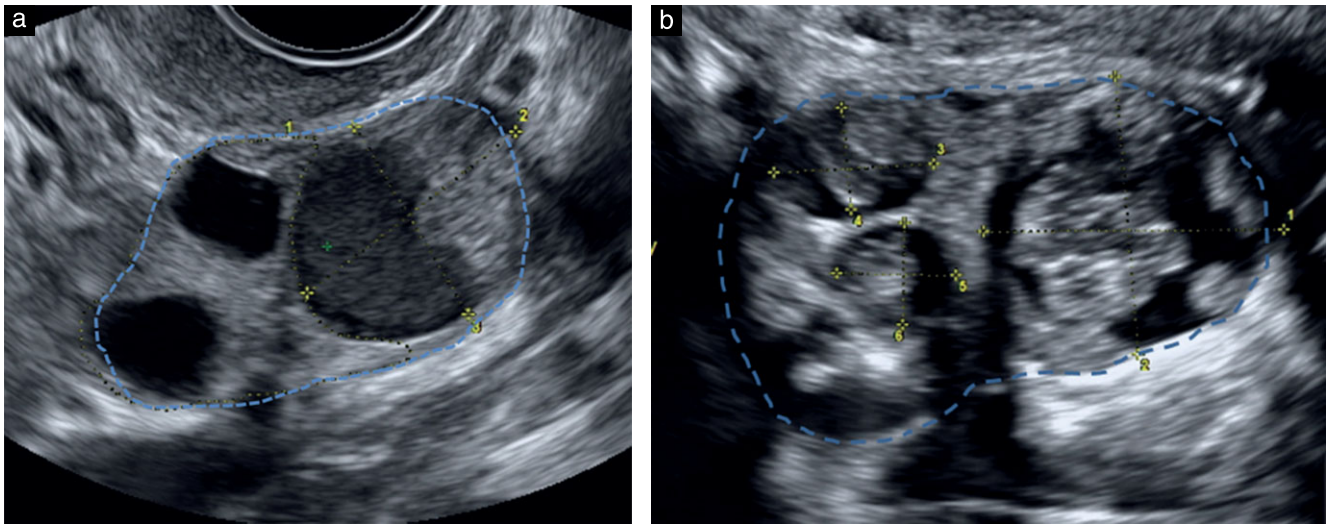

Figure 1 Ultrasound images of serous recurrent borderline ovarian tumor. (a) Single recurrent lesion surrounded by normal ovarian parenchyma (ovarian crescent sign). (b) Multiple recurrent lesions within the ovary.

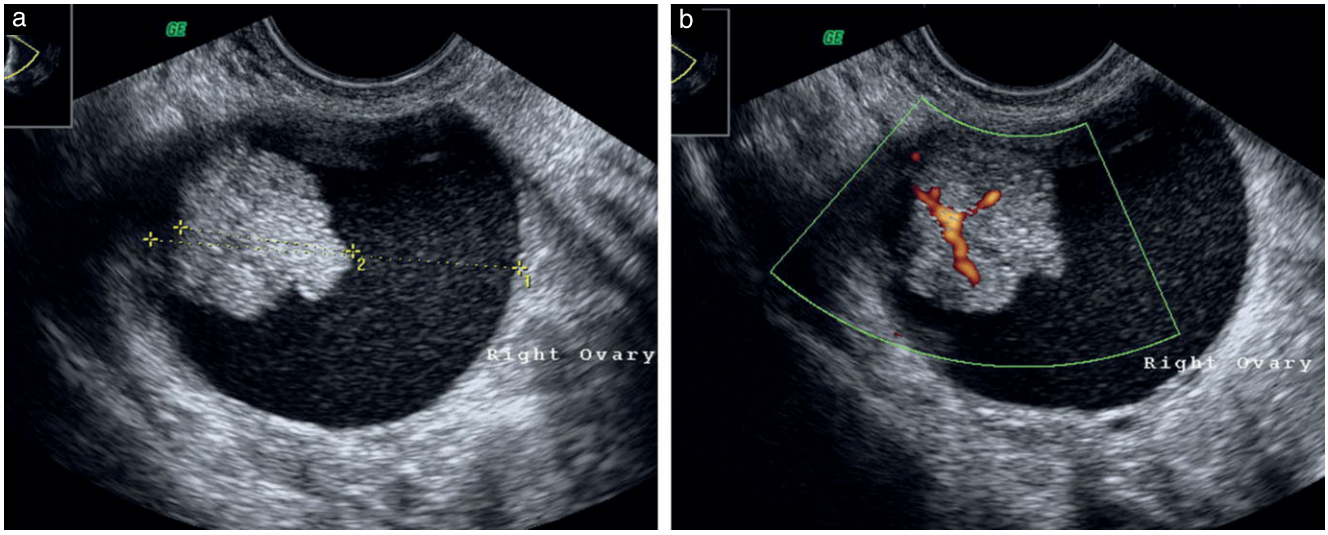

Figure 2 Ultrasound images of serous borderline tumor recurrence. (a) Gray-scale ultrasound image showing a unilocular solid tumor with low-level echogenic cyst contents and a papillary projection with irregular surface. (b) Power Doppler image showing the papillary projection to be moderately vascularized. The ultrasound examiner was confident that the ovarian lesion was a recurrent borderline tumor.

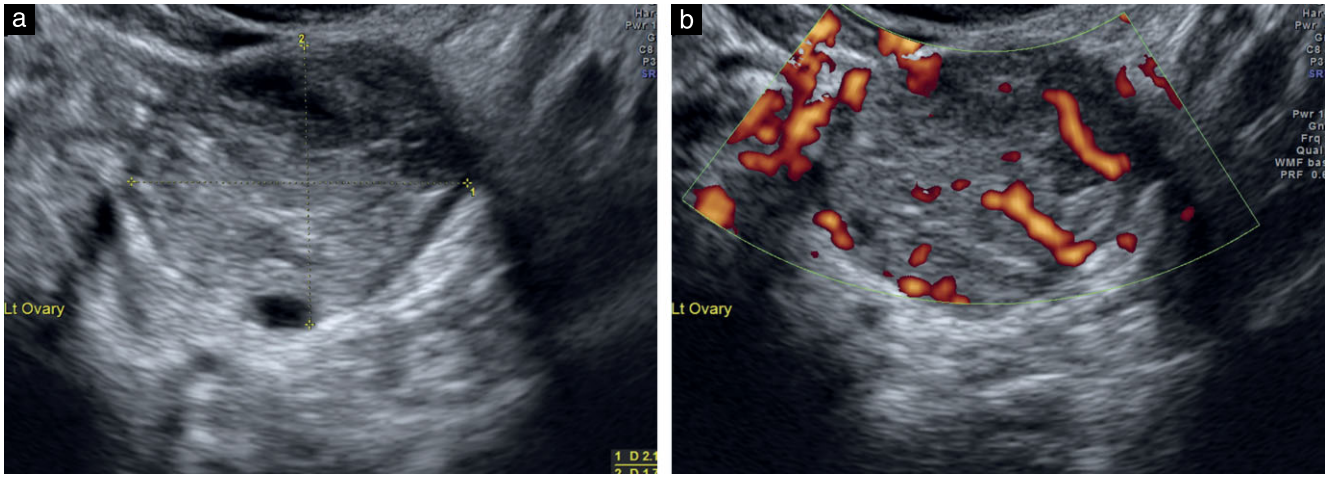

Figure 3 Ultrasound images of serous borderline tumor recurrence with atypical ultrasound appearance. (a) Gray-scale ultrasound imaging revealed a tumor that appeared to be solid. (b) Vascular pattern at power Doppler ultrasound examination of same tumor.

Table 2 Ultrasound findings in 68 patients with recurrent borderline ovarian tumor (BOT)* and diagnosis suggested by ultrasound examiner

Variable	*SBOT (n = 62)*	*Endocervical type MBOT (n = 2)*	*Intestinal type MBOT (n = 4)*	*All (n = 68)*
Largest diameter (mm)	31 (11–106)	37.5 (27–48)	58 (47–80)	32 (11–106)
Type of tumor				
Unilocular	2 (3)	0	0	2 (3)
Unilocular solid	49 (79)	1 (50)	0	50 (73)
Multilocular	2 (3)	1 (50)	3 (75)	6 (9)
Multilocular solid	8 (13)	0	1 (25)	9 (13)
Solid	1 (2)	0	0	1 (1.5)
Number of lesions suspected to be recurrent in same ovary				
1	43 (69)	2 (100)	4 (100)	49 (72)
2	9 (15)	0	0	9 (13)
3	6 (10)	0	0	6 (9)
4–6	4 (6)	0	0	4 (6)
Number of locules				
0	1 (2)	0	0	1 (1.5)
1	51 (82)	1 (50)	0	52 (76.5)
2	2 (3)	1 (50)	0	3 (4.5)
3	4 (6.5)	0	3 (75)	7 (10)
4–10	4 (6.5)	0	0	4 (6)
>10	0	0	1 (25)	1 (1.5)
Number of papillations				
0	3 (5)	1 (50)	3 (75)	7 (10)
1	30 (48)	1 (50)	1 (25)	32 (47)
2	6 (10)	0	0	6 (9)
3	8 (13)	0	0	8 (12)
>3	15 (24)	0	0	15 (22)
Height of largest papillation, if papillation was present (mm)†	14 (3–35)	10	23	14 (3–35)
Irregular papillations‡	55/59 (93)	0	0	55 (93)
Papillation flow present¶	41/56 (73)	1 (100)	0	42/57 (74)
Echogenicity of cyst fluid				
Anechoic	29 (47)	0	1 (25)	30 (44)
Low-level	21 (34)	1 (50)	3 (75)	25 (37)
Ground glass	3 (5)	0	0	3 (4)
Hemorrhagic	0	0	0	0
Mixed	0	1 (50)	0	1 (1.5)
No cyst fluid	1 (2)	0	0	1 (1.5)
Information not available	8 (13)	0	0	8 (12)
Ovarian crescent sign present	55 (89)	2 (100)	0	57 (84)
Fluid in the pouch of Douglas	22 (35)	1 (50)	1 (25)	24 (35)
Color score				
No color	22 (35)	1 (50)	0	23 (34)
Minimal	14 (23)	—	3 (75)	17 (25)
Moderate	24 (39)	1 (50)	1 (25)	26 (38)
Abundant	0	0	0	0
Not assessed	2 (3)	0	0	2 (3)
Diagnosis suggested by ultrasound examiner				
Benign	1 (2)	0	1 (25)	2 (3)
Malignant	61 (98)	2 (100)	3 (75)	66 (97)
Uncertain	0	0	0	0
Specific diagnosis suggested by ultrasound examiner				
Endometrioma	1 (2)	0	0	1 (1.5)
Borderline	60 (97)	2 (100)	3 (75)	65 (96)
Primary invasive	1 (2)	0	0	1 (1.5)
Not possible	0	0	1 (25)	1 (1.5)

Values are given as median (range) or *n* (%). *If more than one recurrence was suspected in the same ovary or in the same patient (in the case of bilateral lesions) the largest was included in this analysis. †Papillation height was measured in 59 patients with SBOT, in one patient with endocervical type MBOT and in one patient with intestinal type MBOT. ‡Papillation irregularity was assessed in 59 patients with SBOT. ¶Papillation flow was assessed with color Doppler in 57 patients, i.e. in 56 serous BOTs and in one endocervical type MBOT. SBOT, serous borderline ovarian tumor; MBOT, mucinous ovarian borderline tumor.

had a largest diameter of 20 mm or less; the largest recurrences were of the mucinous intestinal type (median, 58 mm; range, 47–80 mm) and the smallest of the serous type, 21% (13/62) of the serous borderline recurrences being no larger than 20 mm. Most of the recurrent serous BOTs were unilocular-solid cysts (Figure 2); 95% of these contained papillary projections and almost half contained multiple papillary projections. The median height of the largest papillary projection was 14 mm (range, 3–35 mm). Most recurrent serous BOTs (55/59, 93%) contained at least one papillary projection with irregular surface, and in most cases (41/56, 73%) at least one papillary projection that was vascularized at color Doppler examination. Five of the six recurrent BOTs of the mucinous type were multilocular or multilocular-solid and two contained papillary projections. The ovarian crescent sign was observed in most ovaries with a recurrence (57/68, 84%) but was absent in seven ovaries with a recurrent serous BOT with a median largest diameter of 53 mm (range, 44–106 mm) and in all ovaries with a recurrent intestinal-type mucinous BOT. Most recurrent tumors (38%) were moderately vascularized, but in 34% no vascularization was detected. No patient had ascites.

Using pattern recognition, the ultrasound examiner correctly diagnosed recurrent BOTs in all but three patients. In one patient, with an intestinal type mucinous BOT, a diagnosis was not possible. Of the two misdiagnoses, one was suspected to be a primary invasive tumor because of its solid morphology (Figure 3) and one was suspected to be an endometrioma because of the ground glass echogenicity of its cyst contents and the absence of papillary projections.

DISCUSSION

We have described ultrasound characteristics of recurrent BOTs. Most recurrent BOTs of the serous type appeared as unilocular-solid lesions with irregular papillary projections vascularized at color Doppler examination. These sonographic features are the same as those reported for primary serous BOTs[27]. The six cases of recurrent mucinous BOTs had ultrasound features mimicking those reported to be typical of primary BOTs of the mucinous type: unilocular solid cyst with papillary projections for endocervical-type and multilocular cyst without papillations for intestinal-type mucinous BOT[27].The strength of our study is the large number of recurrent BOTs examined in different European centers and described in a standardized manner. The largest previously published series describing the ultrasound features of recurrent BOTs comprised 18 recurrent serous BOTs and five recurrent mucinous BOTs examined with ultrasound between 1981 and 1997[28]. A limitation of our study is that it is retrospective. Moreover, the small number of recurrent BOTs of the mucinous type precludes the possibility of determining with certainty the most typical ultrasound features of these recurrences. The small number of recurrent mucinous BOTs is likely to be explained by the fact that mucinous BOTs are more rare than serous BOTs in Western countries[29], that many primary mucinous BOTs are so large at diagnosis that cystectomy is not an option[27] and that mucinous BOTs seem to have a recurrence rate lower than that of serous BOTs[30,31]. A further weakness of the study is that we have no information on the ultrasound appearance of the primary BOTs in this series.

Ultrasound morphology of the recurrent BOTs in our study agrees with the results of Zanetta *et al.*[28] who described recurrent BOTs to be cystic with papillae and a well defined capsule. However, papillary projections were found in only 52% (12/23) of the recurrent BOTs in their study *vs* 90% (61/68) in ours. A higher proportion of mucinous recurrences in the study by Zanetta and coworkers[28], as well as the use of older ultrasound equipment with poorer resolution, might explain this discrepancy. Our results also confirm the results of Zanetta *et al.*, i.e. that CA 125 is not helpful in the diagnosis of recurrent BOTs[28], with 71% of our patients having values that did not exceed the commonly used upper limit of normality (35 U/mL).

In our study, recurrent BOTs with a very small diameter were detected at scheduled ultrasound follow-up examinations after fertility-sparing surgery. We believe that awareness of the sonographic appearance of recurrent BOTs can contribute to optimal management of young women with recurrent BOTs . The ability of ultrasound to detect very small recurrences within normal ovarian parenchyma makes it potentially possible to perform repeat fertility-sparing surgery with preservation of an adequate amount of functioning ovarian parenchyma. Our results suggest that an ovarian cyst with papillary projections in a woman with a previous serous BOT is likely to be a recurrence. To minimize the risk of overdiagnosis, it is probably wise to perform follow-up scans in the proliferative phase of the menstrual cycle, because irregularities in the wall of a corpus luteum cyst might lead, theoretically, to a false-positive diagnosis of recurrent BOT.

It is important to emphasize that this study is a pictorial essay describing the ultrasound features of recurrent BOTs. It has not been designed to estimate the sensitivity and specificity of ultrasound with regard to recurrent BOT, nor to determine the optimal frequency or duration of follow-up after conservative surgery for BOTs or elucidate the natural history of recurrent BOTs. This can be done only in prospective studies. Given the well-known risk of late recurrences, as reported in the present series that involved 154 months, a prolonged (even lifelong) surveillance of these patients is advisable. In future studies, small recurrent BOTs should be followed up with ultrasound examination to elucidate their natural history, e.g. their growth rate. Since searching during surgery for a small recurrence hidden inside the ovary might entail a greater risk of damaging the remaining healthy ovarian parenchyma than if the lesion is clearly visible, the optimal time for surgery is probably when the recurrent tumor is large enough to be easily detected macroscopically.

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