GYNECOLOGY

Ultrasonographic diagnosis and longitudinal follow-up of recurrences after conservative surgery for borderline ovarian tumors

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BACKGROUND: Borderline ovarian tumors are generally diagnosed in young women. Because of the young age of patients at first diagnosis and at recurrence, and given the good prognosis of borderline ovarian tumors, a conservative surgical approach in those women who wish to preserve their fertility is advised. In this scenario, transvaginal ultrasound examination plays a key role in the detection of borderline ovarian tumor recurrence, and in assessment of amount of normal functioning parenchyma remaining. To date, no data are available about the natural history of borderline ovarian tumor recurrence.

OBJECTIVE: The aim of the study was to determine growth rate of recurrent ovarian cysts by a scheduled follow-up by ultrasound examination, in women previously treated with fertility-sparing surgery due to borderline ovarian tumors.

STUDY DESIGN: In this prospective observational study, we collected data from 34 patients previously treated with fertility-sparing surgery due to borderline ovarian tumors, who had a suspicious recurrent lesion. The patients underwent transvaginal ultrasonographic examination every 3 months, until the clinical setting recommended proceeding with surgery. According to cyst size at study entry, they were categorized into 3 groups: $\leq$10 mm, 10-20 mm, and >20 mm. Summary statistics for cyst size, growth rate, and the probability of remaining within the same dimension category at first ultrasound during the follow-up were also obtained. For each cyst the growth rate was calculated as the slope of the linear interpolation between 2 consecutive measurements.

RESULTS: Follow-up timing ($P < .001$), cyst size ($P < .001$), and micropapillary pattern ($P < .001$) were factors significantly affecting the cyst growth both in univariate and multivariate analysis. According to size category at first ultrasound, growth rate ranges from a minimum of 0.06 mm/mo for cysts <10 mm up to 1.92 mm/mo for cysts >20 mm. The final histology of all recurrent lesions confirmed the same histotype of primary borderline ovarian tumors.

CONCLUSION: This article represents the first observational study that describes the trend in the growth rate of borderline ovarian tumor recurrence in relation to their size detected at the first ultrasound examination. The findings of this study seem to confirm, in selected patients, that a thorough ultrasonographic follow-up of borderline ovarian tumor recurrence has proven to be safe and feasible. The final goal of such management is to maximize the impact on fertility potential of these young women without worsening their prognosis.

Key words: conservative surgery, ovarian borderline tumor, recurrences, ultrasound

Introduction

Borderline ovarian tumors (BOT) account for approximately 10-15% of all ovarian epithelial tumors.[1] These tumors are generally diagnosed in young women,[2] as International Federation of Gynecology and Obstetrics (FIGO) stage I in nearly 70% of the cases, with a 5-year survival rate of 95-97%.[3]

Given the young age at diagnosis and the good prognosis of BOT, a conservative surgical approach in those patients who wish to preserve their fertility is advised.[4,5] Fertility-sparing surgery (FSS) is defined as the preservation of the uterus and of at least part of 1 ovary with a complete staging procedure.[6-8] Although this strategy has proven to be safe and feasible,[9] recurrences have been described in 5-56% of cases.[3,10] Hence, a close follow-up based on scheduled pelvic ultrasounds is mandatory for early identification of any relapse after FSS.[11,12] At transvaginal ultrasound BOT recurrences can be easily identified, within the residual ovarian parenchyma, as unilocular-solid cysts (in case of serous or endocervical-type mucinous borderline tumors) or multilocular masses (in case of mucinous intestinal-type borderline tumors), mimicking the morphological features of the primary tumor.[13]

In the past, standard treatment of recurrences consisted of definitive ablation of internal genital organs.[14] Nowadays, a repeated FSS can be offered to patients of fertile age.[15-18] In this setting, transvaginal ultrasound examination plays a primary role in the detection of BOT recurrence, and in the assessment of the amount of normal functioning parenchyma remaining.[13] Sometimes, small lesions can be encased in the ovary and thus not easily recognizable during surgical exploration, furthermore they may not be identified by conventional imaging modality and therefore left behind. However, delaying the schedule of the surgical procedure could let small recurrences protrude on the ovarian surface and microscopic lesions become visible, but no data are available about the natural history of BOT recurrences.

The aim of this study was to determine the growth rate of recurrent ovarian cysts in women previously treated by FSS due to BOT.

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TABLE 1
Clinical characteristics of 34 patients with recurrent ovarian borderline tumor after conservative surgery

Primary BOT	
Age at diagnosis, y, median (range)	29.0 (14.0–50.0)
Histology	
Serous	32 (94.1)
Mucinous	2 (5.9)
FIGO stage	
I	11 (32.3)
II/III without invasive implants	19 (55.9)
II/III with invasive implants	4 (11.8)
Micropapillarity	
No	20 (58.9)
Micropapillary aspect	8 (23.5)
Micropapillary	6 (17.6)
Surgery of primary BOT	
Unilateral cystectomy	5 (14.7)
Bilateral cystectomy	11 (32.4)
Unilateral oophorectomy	16 (47.1)
Unilateral oophorectomy and contralateral cystectomy	2 (5.9)

Values are n (%) unless otherwise specified.

BOT, borderline ovarian tumors; *FIGO*, International Federation of Gynecology and Obstetrics.

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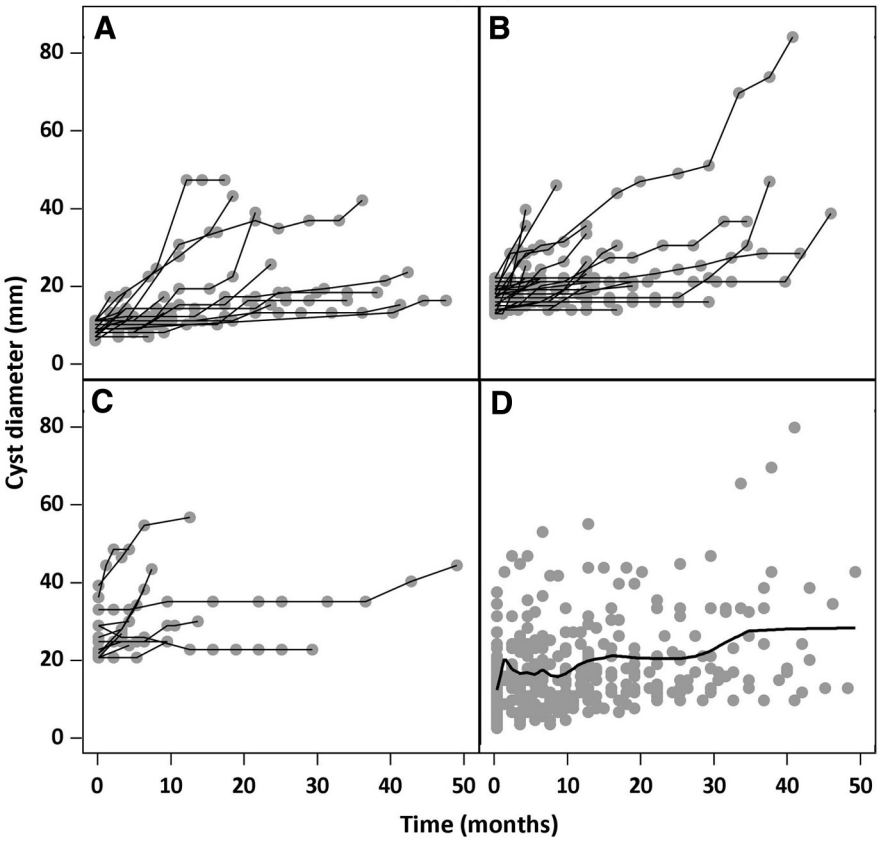
FIGURE 1
Individual cyst profiles during follow-up by category size at first ultrasound



A, <10 mm; **B**, 10-20 mm; **C**, >20 mm; and **D**, overall with overimposed locally weighted scatterplot smoothing function trend line.

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Materials and Methods

A prospective observational study was designed. From October 2000 through December 2011, 34 patients previously treated with FSS due to BOT, who had a suspicious recurrent lesion at follow-up transvaginal ultrasound examination, and with no indication to immediate surgical treatment (Table 1), were enrolled in a prospective protocol of longitudinal surveillance. All patients were followed up for at least 3 months before undergoing surgery. In all, 29 patients were recruited in the Preventive Gynecologic Unit at European Institute of Oncology in Milan, and 5 patients in the Gynecologic Oncology Unit of the University of Sacred Heart in Rome. The review board of both departments approved the study protocol.

All the study patients signed informed consent at enrollment.

All recurrences were detected at the planned follow-up ultrasound examinations. These were scheduled every 3 months for the first 2 years after FSS and every 6 months thereafter.

After the diagnosis of suspicious recurrent lesion, the patients underwent transvaginal ultrasonographic examination and serum biomarker dosage (CA125 and CA19.9) every 3 months, until the clinical setting recommended proceeding with surgery.

All examinations were performed by 2 experienced ultrasound examiners, with 15 years of experience in gynecological oncology ultrasound (D.F. and A.C.T.). High-end ultrasound equipment, 5.0- to 9.0-MHz frequency vaginal probes, and 3.5- to 5.0-MHz frequency abdominal probes were employed. Transvaginal and transabdominal scans were subsequently performed on each patient to ensure a complete examination of the entire pelvic and abdominal cavity.

The following parameters were assessed at any transvaginal ultrasound examination: size of the lesion (3 orthogonal diameters), type of mass (unilocular-solid, multilocular, multilocular-solid, solid), presence and number of papillary projections (defined

TABLE 2
Characteristics of borderline tumor recurrence and indications for surgery

Recurrent BOT (n = 39)	
Age at recurrence, y, median (range)	32.0 (15.0–50.0)
Time from primary diagnosis to considered recurrence, mo, median (range)	34.1 (28.1–39.9)
Time of follow-up of considered recurrence, mo, median (range)	9.8 (3.0–54.0)
Recurrence	
First	16 (41.0)
Second	17 (43.6)
Third	5 (12.8)
Fourth	1 (2.6)
Surgical treatment	
Unilateral cystectomy	26 (66.7)
Bilateral cystectomy	5 (12.8)
Unilateral oophorectomy	4 (10.3)
No conservative treatment	4 (10.3)
No. of recurrent cyst	
1	22 (56.4)
2	8 (20.5)
3	4 (10.3)
4	3 (7.7)
5	2 (5.1)
Extraovarian implants at surgery[a]	
No	17 (44.7)
Not invasive	20 (52.6)
Invasive	1 (2.6)
Indications for surgery	
Cyst related	
Cyst size ≥40 mm	10 (25.6)
Doubling of tumor dimension in 3 mo	3 (7.7)
High no. of cyst	1 (2.6)
High growth rate	3 (7.7)
Disease on ovarian surface	1 (2.6)
Patient related	
Desire of pregnancy	6 (15.4)
Elevated tumor markers	4 (10.3)
Patient request due to subjective anxiety	4 (10.3)
Pregnancy	3 (7.7)
Menopausal	2 (5.1)
Not available	2 (5.1)

Values are n (%) unless otherwise specified.

BOT, borderline ovarian tumors.

[a] Data not available for 1 patient.

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TABLE 3
Ultrasound findings in patients with suspicious recurrent ovarian borderline tumor at study entry

Recurrent cysts (n = 66)	
Cyst largest dimension, mm, mean (SD)	14.4 (7.0)
Height of largest papillation, mm, mean (SD)	7.7 (3.7)
Type of cyst	
Unilocular-solid	62 (93.9)
Multilocular-solid	4 (6.1)
Diameter, mm	
≤10	23 (34.8)
10–20	30 (45.6)
21–30	10 (15.1)
>30	3 (4.5)
No. of locules	
1	62 (93.9)
2	2 (3)
>4	2 (3)
No. of papillations	
1	55 (83.3)
2	6 (9.1)
3	3 (4.6)
4	2 (3.0)
Echogenicity of cyst fluid	
Anechoic	22 (33.3)
Low level	22 (33.3)
Ground glass	22 (33.3)
Papillation flow present	29/60 (48.3)
Color score	
Absent	31 (47.0)
Minimal	8 (12.1)
Moderate	21 (31.8)
Not assessed	6 (9.1)

Values are n (%) unless otherwise specified.

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as any solid protrusion into a cyst cavity with a height of ≥3 mm),[19] number of locules, echogenicity of cyst fluid, irregularity of the surface of papillary projections, and presence of solid tissue other than papillary projections. The color content of the papillary projections at power Doppler examination was estimated subjectively by the ultrasound examiner using a color score as described by Timmerman et al[19] (1 = no vascularization; 2 = minimal vascularization; 3 = moderate vascularization, 4 = high vascularization).

The tumor pattern recognition method was used to make a diagnosis of suspicious recurrence. Morphological features suggestive of recurrences of BOT were: unilocular-solid cysts with at least 1 papillary projection for serous or mucinous endocervical-type BOT, and multilocular cyst without papillations for intestinal-type mucinous borderline tumor.[13] Rarely, recurrent lesions appear as unilocular, multilocular-solid cysts with papillary projections, or as solid masses.[13]

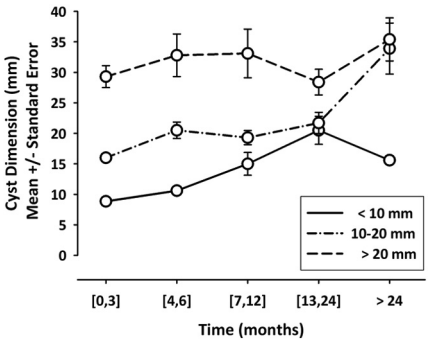
Young patients wanting to preserve fertility but with no immediate pregnancy plan were offered a follow-up program if fulfilling the following criteria: no evidence of metastasis, no ascites, maximum diameter of the suspected recurrent lesion <40 mm, presence of healthy ovarian tissue adjacent to the tumor (namely "ovarian crescent sign"),[20,21] and negative tumor marker (CA125, CA19.9). Evidence of multiple recurrent lesions did not represent an exclusion criterion and all individual lesions were considered for the analysis.

Patients were offered a further FSS when the following criteria were met: desire of pregnancy, patient's request due to subjective anxiety, tumor markers above the upper normal limit, rapidly increased growth rate of the cyst defined as doubling of tumor dimension in 3 months, and cyst size ≥40 mm. Definitive surgery was performed in case of patients' choice, no more pregnancy desire due to age, no more evidence of disease-free ovarian tissue, presence of ascites, or detection of peritoneal implants. All the patients enrolled in this study eventually underwent surgery.

Statistical analysis

Patients characteristics, surgical procedures, and cyst ultrasound features were tabulated and summarized using counts and percentages; continuous variables were expressed by mean, median, SD, and range as appropriate. According to cyst size at study entry, they were categorized into 3 groups: <10 mm, 10-20 mm, and >20 mm. Summary statistics for cyst size, growth rate, and the probability of remaining within the same dimension category at first ultrasound during the follow-up were also obtained. To take into account the influence of the cyst size on the growth rate, at each follow-up time,

FIGURE 2
Cysts dimension by follow-up time



Mean cyst size by follow-up time according to size at first ultrasound.

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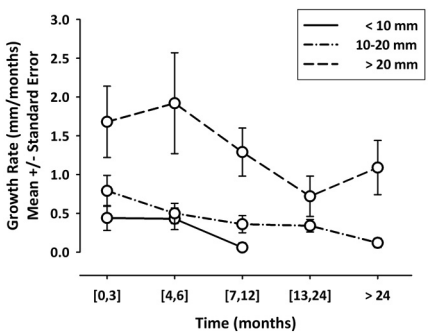
cysts were reallocated to the new size category if their dimension exceeded the limits of the category at the first visit. For each cyst the growth rate was calculated as the slope of the linear interpolation between 2 consecutive measurements.

Both univariate and multivariate hierarchical mixed model were constructed to identify determinants of growth rate using time visit as random effect and the log-normal link function. Bayesian information criteria was used for model selection. Cysts were nested within patient. Covariables were age, histology, extraovarian implant, micropapillarity, and number of recurrences. Diameter category (<10 mm, 10-20 mm, and >20 mm) entered the model as a time-dependent covariate. Differences in follow-up durations by diameter at first visit were tested for bias selection using the Kruskal-Wallis test. A panel plot of individual profile growth curves by diameter at baseline was produced (Figure 1). Median time to indication for surgery with 95% confidence interval was estimated by the Kaplan-Meier method. Reaching a cyst size of 40 mm was considered the threshold for surgery. Patients who underwent surgery for reasons other than cyst size upper cut-off were censored. All tests were 2-tailed and considered statistically significant at the alpha level of 0.05.

All analyses were conducted using software (SAS System 9.2 for Windows, SAS Institute Inc, Cary NC).

FIGURE 3
Cysts growth rate by time



Cyst growth rate curves by follow-up time according to size at first ultrasound.

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TABLE 4
Cyst dimension and cyst growth rate by follow-up time according to their size category

Dimension category at first ultrasound, mm	Follow-up time, mo	N	Growth rate, mm/mo, mean (SE)	Sojourn probability, %[a]
<10	0–3	20	0.44 (0.16)	87.0
	4–6	10	0.43 (0.14)	43.5
	7–12	6	0.06 (0.06)	26.1
	13–24	—	—	0[b]
	>24	—	—	0[b]
10–20	0–3	30	0.79 (0.20)	90.0
	4–6	22	0.50 (0.13)	56.7
	7–12	20	0.36 (0.11)	43.3
	13–24	13	0.34 (0.08)	23.3
	>24	7	0.12 (0.06)	6.7
>20	0–3	16	1.68 (0.46)	100
	4–6	17	1.92 (0.65)	84.6
	7–12	16	1.29 (0.31)	53.8
	13–24	11	0.72 (0.26)	23.1
	>24	8	1.09 (0.35)	15.4

[a] Probability of not changing initial size category with time; [b] Not observed.

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Results

A total of 34 patients with a diagnosis of BOT recurrence were prospectively followed up by transvaginal ultrasound at our institutions.

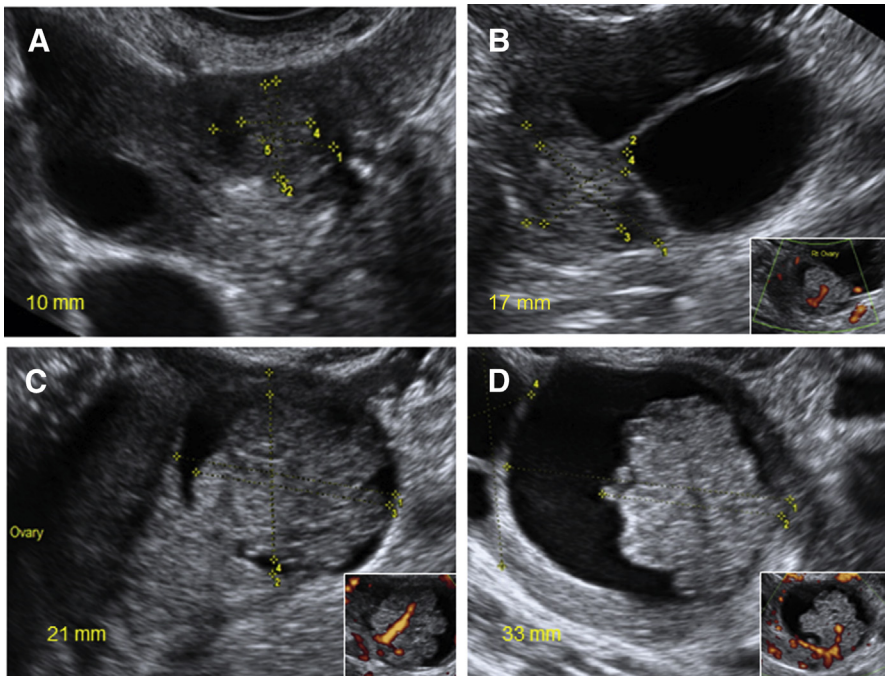
Clinical characteristics of the patients at study entry are shown in Table 1. All patients were premenopausal and age <40 years except 1. Median time from primary diagnosis to diagnosis of suspicious BOT recurrence was 34.1 months. The primary tumor was serous BOT in 32 (94.1%) patients and mucinous endocervical type in 2 (5.8%) patients.

At the diagnosis of the primary tumor, 23 (67.6%) patients were FIGO stage II and III, with invasive implants in 4 (11.8%) cases (Table 1). In 14 (41.2%) patients micropapillarity pattern was described at initial pathology.

Of these 34 patients, 16 underwent cystectomy at first surgery therefore preserving both ovaries, whereas 16 had a monolateral salpingo-oophorectomy and 2 a monolateral salpingo-oophorectomy with contralateral excision of a borderline cyst.

Recurrences were almost all monolateral (71.8%). Namely, recurrence was detected on the same ovary already

FIGURE 4
Ultrasound images of a unilocular-solid serous borderline ovarian tumor recurrence



This borderline ovarian tumor recurrence was diagnosed at 10 mm and reached 33 mm in 1 year before further fertility-sparing surgery. **B-D**, Typical vascular tree.

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treated by conservative surgery at the first diagnosis in 8 (20.5%) patients, on the contralateral ovary in 20 (51.2%) patients, and bilaterally in 11 (28.2%) patients.

Sixteen (45.7%) patients were at their first recurrence, 17 patients had experienced 1 previous recurrence, 5 patients had experienced 2 previous recurrences, and 1 was diagnosed at her fourth recurrence. Five patients were followed up for 2 consecutive recurrences, thus a total of 39 events were evaluated in our analysis (Table 2).

The enrolled patients were prospectively followed up by transvaginal ultrasound for a median time of 9.8 months (range 3-54 months) prior to a further surgical procedure. Patients with cyst size <10 mm and 10-20 mm at first ultrasound had both a median follow-up of 12 months, whereas it was 7 months for those with cyst size >20 mm. No statistically significant difference was observed between these 2 medians of time ($P = .31$), thus excluding an observation length bias related to cyst size.

Ten (25.6%) cysts met the criterion for surgical treatment as reaching the upper limit size of ≥40 mm and 3 (7.7%) had a doubling of tumor dimension within 3 months, whereas pregnancy desire and/or anxiety were the reasons for surgery in other 6 (15.4%) and 4 (10.3%) patients, respectively.

A further indication for surgery in 4 (10.3%) patients was the observation of biomarker value above the upper limit (Table 2).

The final histology of all recurrent lesions confirmed the same histotype of primary BOTs.

Ultrasound findings at study entry are shown in Table 3. The most common ultrasonographic feature of BOT recurrence was the presence of unilocular-solid cyst (93.9%), with a mean of the largest diameters, at the initial evaluation, of 14.4 ± 7.0 mm (Table 3).

Endoluminal papillae were always detectable, ranging between 1-4 in each cyst, even in case of a very small cyst. The mean height of the largest papillary projection was 7.7 ± 3.7 mm, with irregular surface in all cases. The typical vascular tree was not detectable in papillae <5 mm in size (6; 9.1%), being the color score at entry study absent in 31 (47%) cysts, while minimal or moderate color score was observed in 29 (43.9%) cysts (Table 3).

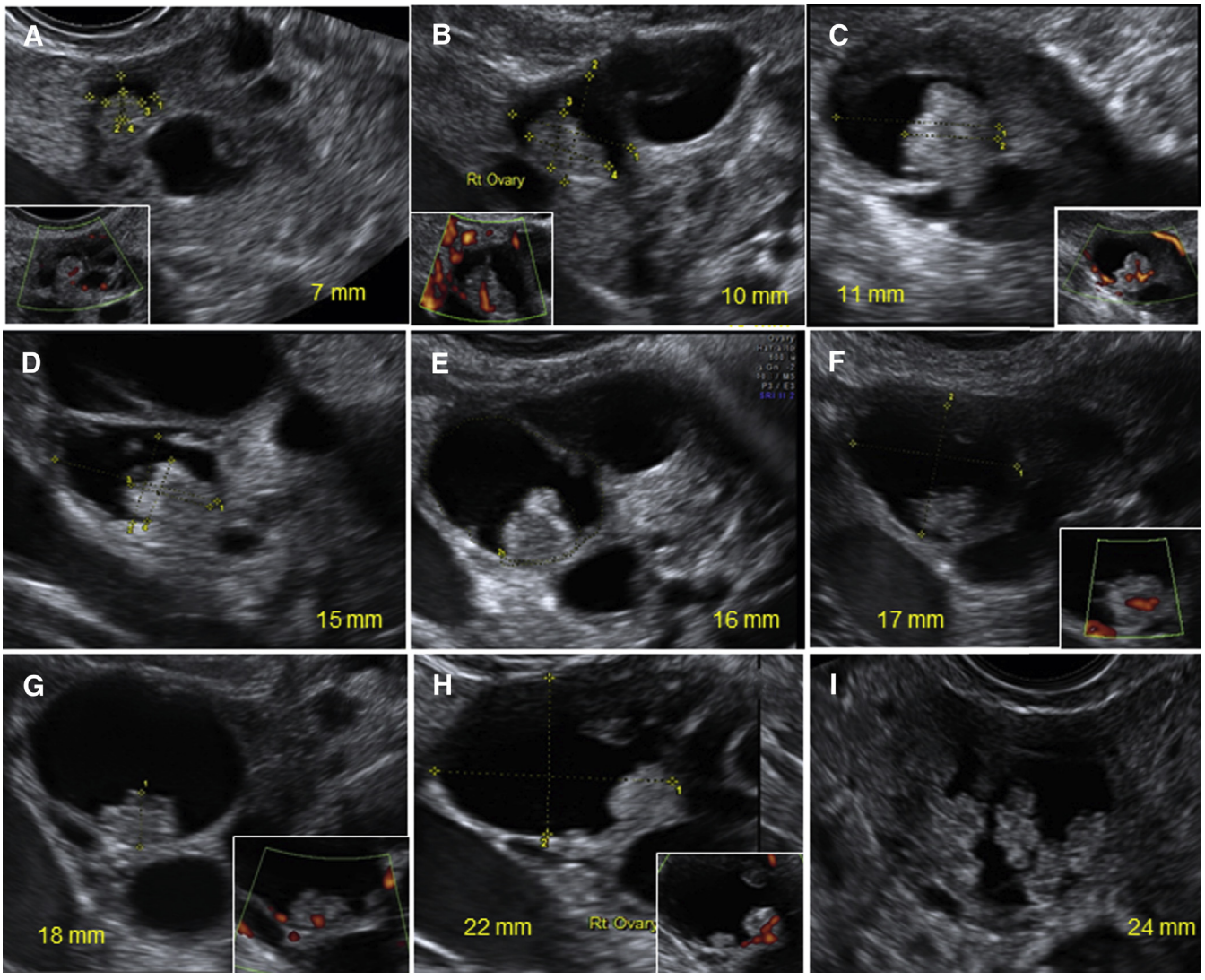
Follow-up timing ($P < .001$), cyst size ($P < .001$), and micropapillary pattern ($P < .001$) were the factors significantly affecting cyst growth both in univariate and multivariate analysis. In univariate analysis and in the best multivariate explanatory model, number of previous recurrences ($P = .225$ and $P = .972$ respectively), FIGO stage at initial presentation ($P = .775$ and $P = .053$, respectively), histology ($P = .180$ and $P = .176$, respectively), and invasive implants ($P = .122$ and $P = .106$, respectively) were not statistically significant. On the contrary, age was not significant in univariate analysis ($P = .204$) but it was significant in multivariate analysis ($P < .001$).

Figure 1 shows the individual cyst profiles according to the size category at the entry study and overall trend of cyst growth. Figures 2 and 3 show the average cyst growth and the growth rate during the follow-up period, respectively. While the average dimension over time seems to increase linearly for each category (Figure 2) the growth rate shows a nonlinear decrease that depends on the cyst size and time (Figure 3).

According to size category at first ultrasound, the range of growth rate varies from a minimum of 0.06 mm/mo for cysts <10 mm up to 1.92 mm/mo for cysts >20 mm (Table 4). Figures 4 and 5 show 2 recurrent BOTs with a different growth rate and followed up for 12 month and 5 years, respectively, before a further FSS.

Table 4 shows the probability of remaining in the same size category with time. Cysts with a diameter <10 mm at first ultrasound have 87% probability of not exceeding 10 mm within 3 months, 43.5% within 6 months, and 26.1% within 1 year. Cysts in the 10-20 mm range at first ultrasound examination

FIGURE 5
Ultrasound images of a low-growing borderline ovarian tumor recurrence



Selected ultrasound images of unilocular-solid serous borderline ovarian tumor recurrence. Low growth rate, ranging from 7 mm at diagnosis to 29 mm in 5 years, is shown before further fertility-sparing surgery. **A**-**C**, **F**-**H**, Typical vascular tree is evident also in very small papillae.

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have higher probabilities to remain in the same category than those not exceeding 10 mm, whereas cysts >20 mm have even higher chances of being in the same size category at each interval time considered. This could be explained by the fact that cysts belonging to the first size category were on average closer to the upper limit of 10 mm (mean distance 2.86 ± 1.17 mm); for intermediate cysts the mean distance was 6.74 ± 2.97 mm and for the cysts in the size category >20 mm, was 14.38 ± 6.54 mm. This could justify why the smaller cysts, despite a lower growth rate, have a higher probability of moving to the next category than larger cysts, characterized by a higher growth rate.

In our case series median time from diagnosis to surgery (ie, time for a cyst to reach 40 mm size) was 43.5 months (95% confidence interval, 21.1—not estimable).

Comment

This article represents the first observational study that describes the trend in the growth rate of BOT recurrences in relation to their size at the first ultrasonographic detection. The findings of this study seem to confirm that, in selected patients, a thorough ultrasonographic follow-up of BOT recurrences has proven to be safe and feasible.

The main strength of the study is that this represents the first prospective study on longitudinal surveillance of BOT recurrences after FSS with an adequate follow-up period, providing new relevant information for the conservative management of BOTs. Moreover, all the transvaginal ultrasound examinations

have been performed by examiners with a specific interest and long experience in gynecologic oncology ultrasonography. However, the main limitations are in the relatively small population sample and in the relatively short follow-up to verify a possible impact on the oncology outcomes.

The small number of recurrent mucinous borderline tumors precludes the possibility to determine the growth rate of these type of recurrences. Such a small number is likely due to the fact that in Western countries mucinous BOTs are uncommon compared to serous ones,[22] that many of them have such a large size at diagnosis that cystectomy is not an option,[22] and that they seem to have a lower recurrence rate than serous counterparts.[23,24]

As already described in our previous article,[13] the sonographic features of BOT recurrences are the same as those reported for primary serous borderline tumors.

Knowledge of the sonographic appearance of recurrent BOT and their growth rate can help physicians to optimally treat young women with recurrent BOTs. The ability to detect very small recurrences encased in normal ovarian parenchyma allows repeated FSS while preserving an adequate amount of functioning ovarian tissue. In case of lesions with a diameter <10 mm a close follow-up scan should be performed to minimize the risk of overdiagnosis, excluding functional ovarian cysts.

Optimal time of surgery seems to be when the recurrent tumor is large enough to be easily detected macroscopically, since small recurrences hidden within the ovary might entail a greater risk of damaging the remaining healthy parenchyma.

To our knowledge, there are no publications on the prospective observation of the growth rate of recurrent BOTs. Zanetta et al[25] reported in 2001 the ultrasonographic description of BOT recurrences, however without any data on longitudinal follow-up.

The findings of this prospective study may have a clinical impact on the management of BOT recurrence after FSS in selecting both those patients who may need surgery shortly after the diagnosis of recurrence and those who may have it delayed, therefore reducing the number of surgical interventions. As reported in the literature,[10,15,26] and as shown in our pictorial article,[13] women with a strong desire of future pregnancies may be subjected to repeated FSS for BOT recurrence. The final goal of such a management is to minimize the impact on the fertility potential of these young women without worsening their prognosis.

Our results on the cyst growth rate may be relevant in planning the best surgical approach: patients with previous FSS without an immediate desire of pregnancy and/or with small ovarian cysts suspicious of being BOT recurrences could benefit from an intensive follow-up and a surgical procedure performed close to the planned pregnancy.

The demonstration of their slow growth rate and the reassuring data about the final outcome (none of the studied lesions were invasive at histology) seem to support this strategy.

The identification of a trend in the growth rate of BOT recurrences in relation to their initial size could have a significant clinical impact on the management of BOT recurrences. Cysts that, during the follow-up period, remain within the same curve may be followed up with a more delayed interval schedule and for a longer period of time, whereas cysts that move from one to the next growth curve require a closer follow-up as they reach the surgical cut-off limit of 40 mm in diameter earlier. Moreover, since >50% of BOT recurrences remain within the same growth curve during the first year of follow-up, it seems reasonable and safe to delay surgical intervention and to widen the follow-up interval after verifying that they do not display a fast growth rate.

In conclusion, newly diagnosed suspicious small (<4 cm) ovarian cysts after FSS for BOTs display a slow growth rate, therefore, in selected patients, follow-up of such lesions is feasible and safe. However, prior to recommending this strategy as a routine management of BOT recurrences, a longer follow-up in larger series is necessary. Furthermore, oncologic outcomes of immediate vs delayed and repeated FSS should be adequately addressed in future investigations. ■

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