Predictive features of borderline ovarian tumor recurrence in patients with childbearing potential undergoing conservative treatment

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Abstract. Borderline ovarian tumors (BOT) represent 10-12% of ovarian cancer cases with a higher prevalence in young patients. Although reproductive outcomes are satisfactory after conservative treatment, several authors reported a higher relapse rate in patients undergoing fertility-sparing surgery compared with radical treatment. The aim of the present study was to identify predictive factors of BOT recurrence in patients with childbearing potential undergoing conservative treatment with unilateral salpingo-oophorectomy. From January 2010 to December 2020 all patients with childbearing potential undergoing conservative treatment for early-stage BOT were included in the analysis. Expert sonographers performed the ultrasounds and classified the ovarian lesion according to International Ovarian Tumor Analysis criteria. A total of 230 patients with BOT that underwent surgical treatment during the study period were analyzed. Of these, 82 patients met the inclusion criteria. Relapse was experienced in 11 cases (13.4%), one (1.2%) peritoneal surface and 10 (12.2%) recurrences on the contralateral ovary. Ovarian tumor size >50 mm (P=0.032; OR 7.317; 95% CI 0.89-60.29), multilocular cysts >10 loculi (P=0.016; OR 7.543; 95% CI 1.64-34.78), cysts with >4 papillae (P=0.025; OR 6.190; 95% CI 1.40-27.36) were statistically correlated with recurrent BOT. Overall, the present study showed that lesions with maximum diameter >50 mm (P=0.014), multilocular cysts >10 loculi (P=0.012) and cysts with >4 papillae (P=0.003) were independent predictive factors of BOT recurrence (P<0.001; correlation coefficient R=0.481) in patients with the potential to bear children undergoing conservative treatment.

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Introduction

Borderline ovarian tumors (BOT) represent 10-12% of ovarian cancers with a higher prevalence in young patients (1). An incidence of 4.8 new cases per 100.000 women is reported in Europe (2) with a 13.9% relapse rate in comprehensive surgical treatment cases (3). International guidelines recommend unilateral salpingo-oophorectomy and multiple peritoneal biopsies in patients with childbearing potential who wish to maintain their fertility (4). Minimally invasive or ultra-minimally invasive approaches are feasible in this patient subset (5-8). Although reproductive outcomes are satisfactory after conservative treatment, several authors reported a higher relapse rate in patients undergoing fertility-sparing surgery compared to radical treatment (9,10). Furthermore, Uzan *et al* reported a higher rate of progression to cancer for mucinous and micropapillary BOTs undergoing conservative surgery (11). Therefore, completion surgery after childbearing is often suggested, although not for all BOT histological types (4). In this scenario, early recognition of relapsing cases is a cornerstone for correct management when conservative treatment is pursued (12). Previous studies showed several molecular and pathological features associated with

relapse in BOT patients (13-15). Among these, the micropapillary architecture and microinvasive tumors are the main culprits of recurrence in serous BOTs (16). Abnormal tumor markers, advanced-stage at diagnosis, and cystectomy are factors associated with BOT relapse in radical treatment cases (17). Despite this, valid scientific evidence on BOT recurrence predictors in selected patients undergoing conservative surgery is still lacking.

The aim of this study is to identify predictive factors of BOT recurrence in patients with childbearing potential undergoing conservative treatment with unilateral salpingo-oophorectomy.

Materials and methods

From January 2010 to December 2020 all patients with childbearing potential undergoing conservative treatment for early-stage BOT at the University Hospital of Parma, at the "Sacro Cuore-Don Calabria" Hospital in Negrar, at the department of gynecologic oncology of the University of Palermo, at the Hospital USL-IRCCS of Reggio Emilia, and the University Hospital of Verona were included in the analysis. Inclusion criteria were age >18 years, patients affected by apparent early International Federation of Gynecology and Obstetrics (FIGO) stage BOT of any histological type, women undergoing conservative treatment with both laparoscopic and laparotomic approaches. Patients of childbearing potential were defined as all patients of any childbearing age wishing to become pregnant. Patients undergoing 'ultraconservative' surgery (cystectomy), patients undergoing bilateral salpingo-oophorectomy, and cases with missing clinical-pathological data were excluded from the analysis. Conservative treatment was defined as conservation of at least a portion of one ovary and the uterus. Clinical and demographic characteristics, ultrasound aspects of the ovarian lesion, intraoperative data, and postoperative instrumental investigations were analyzed of all patients meeting inclusion criteria. Preoperative assessment included transvaginal gynecological ultrasound, computed tomography (CT), and neoplastic markers. Expert sonographers with at least 10 years of experience performed the ultrasounds and classified the ovarian lesion according to International Ovarian Tumor Analysis (IOTA) criteria (18). According to international guidelines, conservative treatment meant unilateral salpingo-oophorectomy with peritoneal biopsies and peritoneal washing (4). The open vs. minimally invasive surgical approach was chosen relating the tumor size and the risk of intraoperative cyst rupture (19). In the case of laparoscopic surgery, an endobag was used to safely remove the ovarian lesion avoiding tumor spillage. Gynecological examination with transvaginal ultrasound and neoplastic markers were performed during the follow-up period. CT scan was required annually or in case of neoplastic markers alteration. Ca125 testing was carried out four times a year for the first two years and two times a year thereafter. All patients before surgery gave their written consent to the surgical procedure and the use of their anonymous data for scientific purposes. The study was approved by the ethics committee of the University Hospital of Parma.

Statistical analysis. Quantitative variables are expressed in median with range. The associations between categorical variables were analyzed using Chi-square or the Fisher exact test when required. The identification of the independent variables associated with BOT recurrence (dependent variable) was performed by linear regression. Odds Ratio (OR) and 95% confidence interval (CI) were reported for statistically significant variables. A logistic regression model was used to identify the variables with a P-value <0.05 in univariate analysis correlated to the BOT recurrence. A P-value <0.05 was considered statistically significant. Analyzes were performed using SPSS 25 (IBM Corp.).

Results

Two hundred thirty BOT patients undergoing surgical treatment during the study period were analyzed. Of these, 82 patients met the inclusion criteria. Relapse was experienced in 11 cases (13.4%), one (1.2%) peritoneal surface, and 10 (12.2%) recurrences on the contralateral ovary. Median age was 33.5 years, range 31 (18-49), median Body Mass Index (BMI) was 23.0 kg/m^2, range 33 (17-50), and median follow-up was 42.5 months, range 118 (6-120). Of the 57 women (69.5%) >30 years 9 (15.8%) had relapse (P=0.283), 5 relapses (12.8%) occurred in patients >35 years (P=0.570), and one case (5.6%) of relapse presented in >40 years women (P=0.268). Furthermore, among 12 (14.6%) obese patients (BMI >30), 3 (25.0%) had recurrence on the contralateral ovary (P=0.202). Nine nulliparous patients (15.3%) out of 59 cases (72.0%) diagnosed relapse (P=0.350). Furthermore, neither comorbidities (previous cancer P=0.866, hypertension P=0.898, cigarette smoking P=0.446), nor previous surgical interventions (ovarian cyst enucleation P=0.216, appendectomy P=0.236, caesarean section P=0.599), nor intraoperative tumor spillage (P=0.586), nor increased neoplastic markers (Ca125 P=0.510, Ca 19-9 P=0.608, Ca 15-3 P=0.233, CEA P=0.444) showed a statistically significant correlation with BOT recurrence. Detailed clinical anamnestic correlations of BOT patients with disease relapses are shown in Table I.

Analyzing the ultrasound characteristics of ovarian lesions, the mean tumor diameter was 93.6 mm (standard deviation 68.53). Ovarian tumor size >50 mm (P=0.032, OR 7.317, 95% CI 0.89-60.29), Multilocular cysts >10 loculi (P=0.016, OR 7.543, 95% CI 1.64-34.78), cysts with >4 papillae (P=0.025, OR 6.190, 95% CI 1.40-27.36) were statistically correlated with recurrent BOT (Fig. 1). In contrast, the solid component diameter > 10 mm (P=0.526), the regular vs. irregular cyst surface (P=0.505), and the color score (P=0.581) showed no correlation with recurrence. The sonographic characteristics of ovarian lesions are summarized in Table II. Besides, surgical approach (laparoscopy vs. laparotomic approach P=0.451), histological subtype (serous P=0.283, mucinous P=0.350, others P=0.748), and FIGO stage (IA P=0.425, IC P=0.281, IIIC P=0.444) did not influence recurrence. Finally, logistic regression analysis showed lesions with maximum diameter >50 mm (P=0.014), multilocular cysts >10 loculi (P=0.012), cysts with >4 papillae (P=0.003) independent predictive factors of BOT recurrence (P<0.001, correlation coefficient R=0.481).

Discussion

The study identified tumor size >50 mm, multilocular cyst >10 loculi, and ovarian cysts with >4 papillae as independent

Table I. Patients' characteristics and correlation with relapse.

Characteristic	Cases (n=82) (%)	Relapse (n=11) (%)	P-value
Age			
>30 years	57 (69.5)	9 (15.8)	0.283
>35 years	39 (47.6)	5 (12.8)	0.570
>40 years	18 (22.0)	1 (5.6)	0.268
BMI >30 (kg/m^2)	12 (14.6)	3 (25.0)	0.202
Previously given birth			
Nulliparous	59 (72.0)	9 (15.3)	0.350
Previous vaginal birth	13 (15.9)	1 (7.7)	0.446
Previous caesarean section	10 (12.2)	1 (10.0)	0.599
Comorbidities			0.400
Previous cancer	1 (1.2)	0	0.866
Smoke	13 (15.9)	1 (7.7)	0.446
Hypertension	3 (3.7)	0	0.898
Previous surgery			0.592
Ovarian cyst enucleation	10 (12.2)	0	0.216
Appendectomy	7 (8.5)	2 (28.6)	0.236
Tumor markers			0.615
Ca125	34 (41.5)	5 (14.7)	0.510
Ca 19-9	11 (13.4)	1 (9.1)	0.608
Ca 15-3	2 (2.4)	1 (50.0)	0.233
CEA	4 (4.9)	1 (25.0)	0.444
Surgical approaches			0.451
Laparoscopy	64 (78.0)	8 (12.5)	
Laparotomy	18 (22.0)	3 (16.7)	
Histology			
Serous	57 (59.5)	9 (15.8)	0.283
Mucinous	23 (28.0)	2 (8.7)	0.350
Others	2 (2.4)	0	0.748
Tumor Spillage	10 (12.2)	1 (10.0)	0.586
Peritoneal Washing	2 (2.4)	1 (50.0)	0.331
FIGO Stage			
IA	61 (74.4)	9 (14.8)	0.425
IC	17 (20.7)	1 (5.9)	0.281
IIIC	4 (4.9)	1 (25.0)	0.444

BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics.

predictors of BOT recurrence in patients with childbearing potential undergoing conservative treatment.

In the literature, conflicting results were reported on the prognostic impact of tumor size in BOT patients (20). Recently, Niu *et al* (3), in a retrospective analysis including both conservative and radical treatment, recognized the ovarian tumor size at diagnosis as associated with increased Ca125 level and recurrence events in BOT cases. Furthermore, in a large prospective study by Kobayashi *et al* (21) involving 6398 Japanese women with an initial diagnosis of endometrioma, the tumor diameter was also an independent risk factor for developing ovarian cancer. As previously hypothesized, possible correlating causes of ovarian tumor size and recurrence would be intraoperative tumor spillage in case of large lesions difficult to mobilize or attached to surrounding structures (22). On the other hand, the large size of the ovarian mass was statistically correlated with the poor diagnostic accuracy of the frozen section due to the pathologist's errors in selecting a sufficient number of anatomical slices for analysis (23). These insufficient pathological samplings could lead to an under-FIGO stage or a missed ovarian cancer diagnosis which could justify the higher relapse rate also in BOT cases. However, few cases of tumor spillage were reported in our series. This result could be justified by the intraoperative use of the endobag in case of minimally invasive treatment. In addition, all surgeries were performed by surgeons experienced in oncological gynecology. Furthermore,

Table II. Ovarian sonographic characteristics and correlation with recurrence.

Characteristic	Cases (n=82) (%)	Relapse (n=11) (%)	P-value
Tumor size >50 mm	51 (62.2)	10 (19.6)	0.032
Solid component			
≥10 mm	33 (40.2)	4 (12.1)	0.526
≥15 mm	27 (32.9)	4 (14.8)	0.521
≥20 mm	20 (24.4)	4 (20.0)	0.260
≥25 mm	17 (20.7)	2 (11.8)	0.592
≥30 mm	15 (18.3)	2 (13.3)	0.678
Cyst surface			0.505
Regular	70 (85.4)	9 (12.9)	
Irregular	12 (14.6)	2 (16.7)	
Color Score			
C1	46 (56.1)	6 (13.0)	0.581
CS 2	24 (29.3)	2 (8.3)	0.305
CS 3	10 (12.2)	2 (20.0)	0.401
CS 4	2 (2.4)	1 (50.0)	0.252
Loculi (number)			
Unilocular	51 (62.2)	4 (7.8)	0.058
>10	9 (11.0)	4 (44.4)	0.016
<10	22 (26.8)	3 (13.6)	0.613
Papillae (number)			
Any	36 (43.9)	2 (5.6)	0.061
<4	36 (43.9)	5 (13.9)	0.581
>4	10 (12.2)	4 (40.0)	0.025

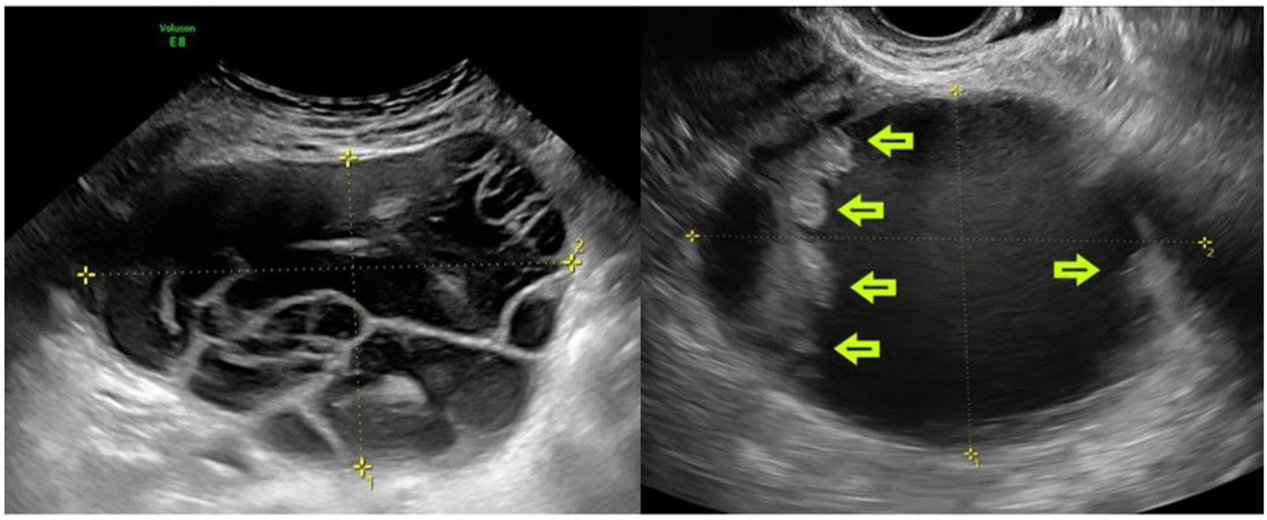

Figure 1. Multilocular cyst (left). Cyst with papillae (right).

an average tumor diameter of less than 10 cm was reported. Therefore, pathologist errors may have been particularly reduced in our study. Indeed, no cases of ovarian cancer misdiagnosis were shown on the frozen section analysis compared to the definitive histological examination in our series.

As known, the multilocular cyst and the presence of papillae are known risk factors for malignancies (24). In an interesting study by Franchi *et al* (25), multilocular or multilocular solid cysts were the most frequent ultrasound manifestations in cases of recurrent BOT. Furthermore, the same authors stated that recurrent ovarian lesions mimicked the same ultrasound multilocular appearance of the primary lesion, especially in mucinous BOTs. Similar results were reported by Zanetta *et al* (26) showing the presence of cysts

with papillae as the most frequent recurring BOT pattern. In line with these authors, our study identified multilocularity and the presence of papillae on the primary lesion as independent predictors of recurrence BOT.

Finally, in contrast with other authors, neither abnormal neoplastic markers level nor FIGO stage predicted BOT recurrence (27). However, selecting only patients with childbearing potential undergoing conservative treatment, we presented extremely homogeneous data with 95.1% of FIGO stage I cases and only 45.1% of patients with abnormal neoplastic markers. These aspects could justify our results.

The present study has the limitations of its retrospective nature. Furthermore, due to the high patient selection, a low number of relapse events were reported. On the other hand, the article could have great clinical relevance, as a closer follow-up of BOT patients with tumor size >50 mm, multilocularity, and the presence of papillae could predict relapse early. Besides, by excluding patients who underwent cystectomy and not reporting cases of intraoperative tumor spillage we reduced the presence of bias influencing recurrence.

In conclusion, the present study showed tumor size >50 mm, multilocularity >10 loculi, and the presence of >4 papillae at the primary ovarian lesions as independent predictors of BOT recurrence in patients with potential childbearing undergoing conservative treatment. Closer follow-up for these patients could be required. Prospective studies would be needed to confirm our findings.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

VAC, SC, MC, GS, VDM, SU, VC, MF and RB conceived and designed the study. ES, LM, AC, GB acquired the data. VAC, RB and VC analyzed and interpreted data. All the authors have read and approved the final manuscript. VAC and RB confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The Ethics Committee of the University Hospital of Parma approved this retrospective study on 12 August 2021.

Patient consent for publication

All patients gave their written informed consent for their anonymized data to be used for scientific purposes.

Competing interests

The authors declare that they have no competing interests.

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