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A clinicopathologic multivariate analysis affecting recurrence of borderline ovarian tumors

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Abstract

Objective. To evaluate the risk factors associated with recurrence of borderline ovarian tumors that may be used as evidence of the efficacy of select preventive procedures.

Methods. Various clinicopathologic factors of 234 patients with borderline ovarian tumors admitted to our hospital between January 2001 and June 2007 were reviewed. Univariate and multivariate logistic regression models were constructed to evaluate the risk factors for odds ratio (OR) and statistical significance. The survival was assessed by the Kaplan–Meier method and proportional hazards model.

Results. Recurrence of borderline ovarian tumors was observed in 26 cases and the median time to recurrence was 29.4 months. Of these cases, 5 occurred involving the ipsilateral ovary, 9 involved the contralateral ovary, and 12 spread to the pelvic peritoneum, including 3 patients who had progressed to invasive carcinoma. No tumor-related deaths were reported. The results of the multivariate logistic regression analysis showed that conservative surgical procedures (OR=2.304; p=0.024), cyst rupture (OR=2.213; p=0.038), advanced FIGO stage (OR=4.114; p=0.000), microinvasion (OR=2.291; p=0.046), and peritoneal implants (OR=2.101; p=0.016) may be independent predictive factors of recurrence. The proportional hazards model identified surgical procedure (relative risk, RR=3.752, p=0.007), cyst rupture (RR=1.985, p=0.006), FIGO stage (RR=3.746, p=0.001), microinvasion (RR=1.153, p=0.009) and peritoneal implants (RR=2.742, p=0.010), as independently related to disease-free survival.

Conclusions. Although patients with borderline ovarian tumors have an excellent prognosis, the risk of recurrence remains. Identification of patients with high-risk factors is essential for offering more selective treatments to prevent recurrence.

Keywords: Borderline ovarian tumors; Recurrence; Risk factors

Introduction

Borderline ovarian tumors, characterized by epithelial proliferation with the absence of stromal invasion, were first described by Taylor in 1929 [1]. Compared to invasive ovarian cancers, borderline ovarian tumors occur in younger women, present at an earlier stage, and have a favorable prognosis. Since laparoscopy has partly replaced the abdominal route in many institutions for the surgical management of adnexal masses in younger patients, the question is whether it is possible to use for fertility-sparing surgery in the management of borderline ovarian tumors. On the other hand, it has been reported that some histopathologic features of borderline ovarian tumors might contribute to recurrence, regardless of what type of surgery is performed [2].

Previously, several investigators have attempted to determine the factors that predispose patients to recurrence of borderline ovarian tumors, but the conclusions remains controversial [2–4]. Many of the studies involved multiple centers, which resulted in assembly biases because of the differences between the hospitals. To clarify the risk factors associated with recurrence of

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borderline ovarian tumors and determine certain preventive procedures in patients presenting with known risk factors, we report here the clinicopathologic data of a large, retrospective study involving patients with borderline ovarian tumors from a single-institution who are representative of western China.

Patients and methods

Two hundred fifty-seven consecutive patients with borderline ovarian tumors treated between January 2001 and June 2007 in the Department of Gynecologic Oncology at West China Second University Hospital of Sichuan University were retrospectively reviewed for clinical characteristics, histopathologic subtypes, surgical types, postoperative chemotherapeutic regimens, the presence or absence of recurrence, and prognosis. Information was acquired by retrospective medical record review and patient interview.

For those women who underwent surgery in our department, the radicality of the surgery was decided on the basis of FIGO stage, the woman's age, and her wish to preserve her fertility. Tumors were graded and classified according to WHO criteria [5]. Staging was according to FIGO classification [6]. The histologic criteria used for the diagnosis of borderline ovarian tumors included the following: (i) stratification of the epithelial lining of the papillae with formation of microscopic papillary projections or tufts arising from the epithelial lining of the papillae; (ii) nuclear atypia; (iii) mitotic activity; (iv) intracystic clusters of free-floating cells; and (v) the absence of stromal invasion. The diagnosis of borderline malignancy was based on an examination of the primary tumor; however, without regard for the presence or absence of extension beyond the ovary. An accurate diagnosis by the pathologist required extensive sampling of the tumor by the pathologist to exclude the presence of invasive elements confidently.

Patients were scheduled for a pelvic examination, blood tests (CA-125 and CA-199 levels), and an ultrasonographic scan of the pelvis every 3 months during the first year following surgery, then every 6 months for 2 years, and finally annually. Twenty-three women were lost to follow-up; the remaining 234 patients were the subjects of our retrospective study.

Statistical analysis

Comparison of sample means was evaluated using analysis of variance. Categorical variables were evaluated using the chi-square test. All of the associated clinicopathologic predictors were used in a logistic regression model with the presence of recurrence as the dependent variable. Because bilateral disease was closely associated with FIGO stage, it was removed from the model. The model was simplified in a stepwise fashion by removing variables that had a p value of >0.05. Survival curves were constructed according to the Kaplan–Meier method and statistical differences between the curves were calculated with the log-rank test. Multivariate survival analysis was performed with the Cox proportional hazards model. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences software, version 11.5 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Borderline tumors comprised 24% of all epithelial ovarian tumors currently occurring in our hospital. The median age for all patients at the time of diagnosis was 40.1 years (range, 14–80 years). In all patients, the serum levels of tumor markers, including CA-125, CA-199, and CEA, were measured preoperatively. There were 145 patients (62%) in whom the CA-125 level was >35 U/ml (the upper limit of normal) and the median value was 107.1 U/mL (range, 4.1–600 U/mL). CA-199 levels were elevated in 26 patients (11%) and varied from 3.2–700 U/mL (median, 84.4 U/mL). CEA levels were elevated in 12 patients (5%) and varied from 27.3–153.2 ng/ml. In patients with mucinous tumors, the preoperative CA-199 was more frequently elevated (17/26; 65%) than the CA-125 level (39/145; 27%; $p=0.001$).

One hundred one tumors were serous (43%), 94 tumors were mucinous (40%), 19 tumors were mixed (8%), 12 tumors were endometrioid (5%), and there were 8 clear cell tumors (4%). The histologic categories and FIGO stages are shown in Table 1. The mean diameter of the serous tumors was 9.3 cm (range, 4–28 cm) with 13 (13%) cases of bilateral lesions. Mucinous tumors averaged 16.6 cm in diameter (range, 5–40 cm) and 22 cases (23%) were bilateral. According to final pathologic diagnoses, we observed 20 cases of micropapillary serous borderline tumors, 13 cases of microinvasion, and 27 non-invasive peritoneal implants (epithelial or desmoplastic). These pathologic features all presented in patients with stage II–III disease.

Treatment

All women in the study underwent surgery as the initial treatment. Among the 234 women with borderline tumors, 182 (78%) underwent laparotomy and 45 (19%) underwent laparoscopy. Seven women had converted to laparotomy because of a suspicion for ovarian cancer and severe adhesions. Conservative treatment, defined as a surgical procedure with conservation of the uterus and salvaging of at least one ovary, was performed in 119 patients (51%). Therefore, four possible types of conservative surgical procedure were performed, as follows: unilateral adnexectomy (UA), UA plus contralateral cystectomy (UA+CC), unilateral cystectomy (UC), and bilateral cystectomy (BC). Among conservative treatment, omentectomy and appendectomy were performed in 24 patients currently. Pelvic lymphadenectomy was performed in 3 patients with stage III disease. When analyzing the type of treatment according to patient age, it was found that conservative treatment was rendered to 86 women (72%) under the age of 40, but to only 33 women (28%) who exceeded this age ($p<0.01$). Radical surgery, defined as bilateral salpingo-oophorectomy with hysterectomy, was performed in 115 patients (49%). Standard staging surgery was performed in 79 patients (34%) and was dependent on the intraoperative frozen histopathologic diagnosis and the patient's age. Staging surgery included peritoneal washings, biopsy of the remaining ovary, omentectomy, appendectomy, multiple peritoneal biopsies, and pelvic

Table 1
Histology and FIGO stages

Histologic type	FIGO stage			Total
	I	II	III	
Serous	66	3	32	101
Mucinous	64	11	19	94
Mixed	15	2	2	19
Endometrioid	10	2	0	12
Clear cell	6	1	1	8
Total (%)	161(69)	19(8)	54(23)	234(100)

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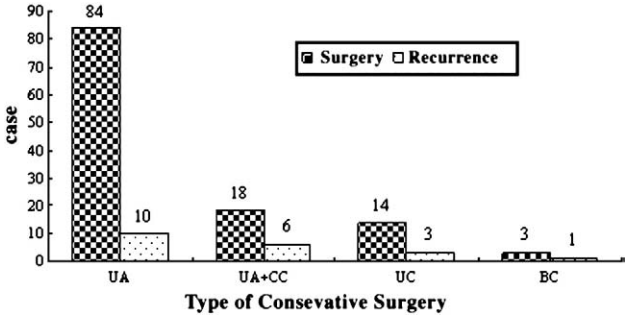

Fig. 1. The relationship between different types of conservative surgery and recurrence.

lymphadenectomy. No patients had lymph node invasion. 14 patients with positive cytologies were encountered.

In our department, all patients underwent transvaginal ultrasound prior to laparoscopy. If the diameter of the cyst was >10 cm, the patients were usually not treated by laparoscopy. When comparing patient characteristics in the laparoscopy and laparotomy groups, we found significant differences between the two groups. First, the mean volume and serum levels of CA-125 in the laparoscopy group were 8.0±2.1 cm and 75.2±11.2 U/ml, respectively, which were significantly lower than in the laparotomy group (13.2±7.1 cm and 114.7±25.6 U/ml, respectively; $p<0.01$). Second, in the laparoscopic group, 16 of 45 patients (36%) had a cyst rupture intraoperatively compared to 20 of 189 (11%) in the laparotomy group. Cyst rupture was more frequent in the laparoscopic group ($p<0.01$). Third, the proportion of women with stage I borderline ovarian tumors (39/45; 87%) was higher in the laparoscopy group than in the laparotomy group (122/189; 65%; $p<0.01$) and all patients had conservative treatment in the laparoscopy group. Finally, the mean age (30.9±13.7 years) was significantly lower and infertility (28.9%) was more frequent in the laparoscopy group than in the laparotomy group (42.3±17.1 years and 2.6%, respectively; $p<0.01$).

Sixty-four women with advanced stage tumors received postoperative chemotherapy. This treatment consisted of 3–4 cycles of cisplatin or carboplatin and cyclophosphamide or 6–10 times of intra-abdominal thiotepa. Some patients received paclitaxel-based combinations as adjuvant treatment.

Follow-up outcome

The median follow-up period was 40 months (range, 8–78 months). The serum CA-125 levels of all patients returned to normal after primary surgery. During follow-up, 26 patients showed a rising CA-125 level and persistent abdominal swelling again. Therefore, second laparotomies were performed in these patients. Recurrences were confirmed by permanent pathologic diagnoses. The median time to recurrence was 29.4 months, with a range of 18–63 months. Among the 26 recurrences, 5 involved the ipsilateral ovary, 9 involved the contralateral ovary, and 12 had spread to the pelvic peritoneum; 3 women had progressed to foci carcinoma (1 serous and 2 endometrioid types). No wound metastases were diagnosed during the study period. No tumor-related deaths were reported. Finally, there were 7 cases of successful delivery after conservative surgery including 2 miscarriages.

The recurrences were unrelated to the surgical approach itself (i.e., laparotomy vs. laparoscopy), but to the type of conservative surgery, such as UA (10/84; 11.9%), UA+CC (6/18; 33.6%), UC (3/14;21.4%), and BC (1/3; 33.3%; Fig. 1). In order to study the possible factors related to recurrence, we analyzed the relationship between recurrence and the associated clinicopathologic risk factors by univariate and multivariate analyses.

Univariate analysis showed a significant association between tumor recurrence with conservative management ($p=0.009$), tumor size ($p=0.022$), cyst rupture ($p=0.009$), bilateral disease ($p=0.001$), FIGO stage ($p=0.006$), micropapillary pattern ($p=0.015$), microinvasion ($p=0.006$), and peritoneal implants ($p=0.003$).The relationship between the clinicopathologic features and recurrence is shown in Table 2.

Multivariate logistic regression was performed for each predictor of the recurrence to calculate odds ratios and 95% confidence intervals. The model was simplified in a stepwise fashion by removing variables that had a p value >0.05.The only five variables that remained statistically significant as independent predictors of the recurrence in the multivariate

Table 2
The relationship between the clinicopathologic features and recurrence

Variables		*N*	BOT recurrences		*P*
			Yes (%)	No (%)	
Age(yrs)	<40	117	18(15.4)	99(84.6)	0.061
	≥40	117	8(6.8)	109(93.2)	
CA-125 (u/ml)	<35	89	7(7.9)	82(92.1)	0.306
	≥35	145	19(13.1)	126(86.9)	
Surgical procedure					
	Conservative	119	20(16.8)	99(83.2)	0.009
	Radical	115	6(5.2)	109(94.8)	
Surgical approach					
	Laparotomy	189	19(10.1)	170(89.9)	0.429
	Laparoscopy	45	7(15.6)	38(84.4)	
Cyst rupture	Yes	36	9(25.0)	27(75.0)	0.009
	No	198	17(8.6)	181(91.4)	
Tumor size (cm)	<10.2	117	7(6.0)	110(94.0)	0.022
	≥10.2	117	19(16.2)	98(83.8)	
Bilateral disease	Yes	35	10(28.6)	25(71.4)	0.001
	No	199	16(8.0)	183(92.0)	
FIGO stage	I	161	11(6.8)	150(93.2)	0.006
	II	19	3(15.8)	16(84.2)	
	III	54	12(22.2)	42(77.8)	
Histology	Serous	101	12(11.9)	89(88.1)	0.946
	Mucinous	94	10(10.6)	84(89.4)	
	Other	39	4(10.3)	35(89.7)	
Micropapillary	Yes	20	6(30.0)	14(70.0)	0.015
	No	214	20(9.3)	194(90.7)	
Microinvasion	Yes	13	5(38.5)	8(61.5)	0.006
	No	221	21(9.5)	200(90.5)	
Peritoneal implants	Yes	27	8(29.6)	19(70.4)	0.003
	No	207	18(8.7)	189(91.3)	
Chemotherapy	Yes	64	7(10.9)	57(89.1)	0.856
	No	170	19(11.2)	151(88.8)	

Other=mixed, endometrioid, and clear cell tumors.

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Table 3
Multivariate analysis of predictors of BOT recurrence

Variables	B	S.E.	*P*	OR	95.0% CI for OR	
					Lower	Upper
Surgical procedure	0.834	0.368	0.024	2.304	1.119	4.742
Cyst rupture	0.794	0.382	0.038	2.213	1.046	4.682
FIGO stage	1.414	0.205	0.000	4.114	2.751	6.154
Microinvasion	0.829	0.416	0.046	2.291	1.013	5.179
Peritoneal implants	0.743	0.307	0.016	2.101	1.151	3.838

analysis were surgery procedure, cyst rupture, FIGO stage, microinvasion, and peritoneal implants. According to the results of the final logistic regression model, the odds ratio (95% confidence interval; p value) of the surgical procedure, cyst rupture, FIGO stage, microinvasion, and peritoneal implants were 2.304 (1.119–4.742; 0.024), 2.213 (1.046–4.682;0.038), 4.114 (2.751–6.154; 0.000), 2.291(1.013–5.179; 0.046), and 2.101 (1.151–3.838; 0.016), respectively. Tumor size and micropapillary pattern could not be used as independent factors in the multivariate model (Table 3).

Survival analysis

Patients with conservative procedure ($P=0.006$) (Fig. 2a), cyst rupture ($P=0.007$), bilateral disease ($P=0.001$), advanced FIGO stage ($P=0.003$), micropapillary ($P=0.012$), microinvasion ($P=0.001$) and peritoneal implants ($P=0.000$) showed a poorer disease-free survival rate (DFS) using univariate Kaplan–Meier survival estimation with log-rank comparisons. However, histologic type (mucinous and non-mucinous) was not a predictor of DFS ($P=0.873$) (Fig. 2b).

The multivariate proportional hazards model identified surgical procedure (RR=3.752, $P=0.007$), cyst rupture (RR=1.985, $P=0.006$), FIGO stage (RR=3.746, $P=0.001$), microinvasion (RR=1.153, $P=0.009$) and peritoneal implants

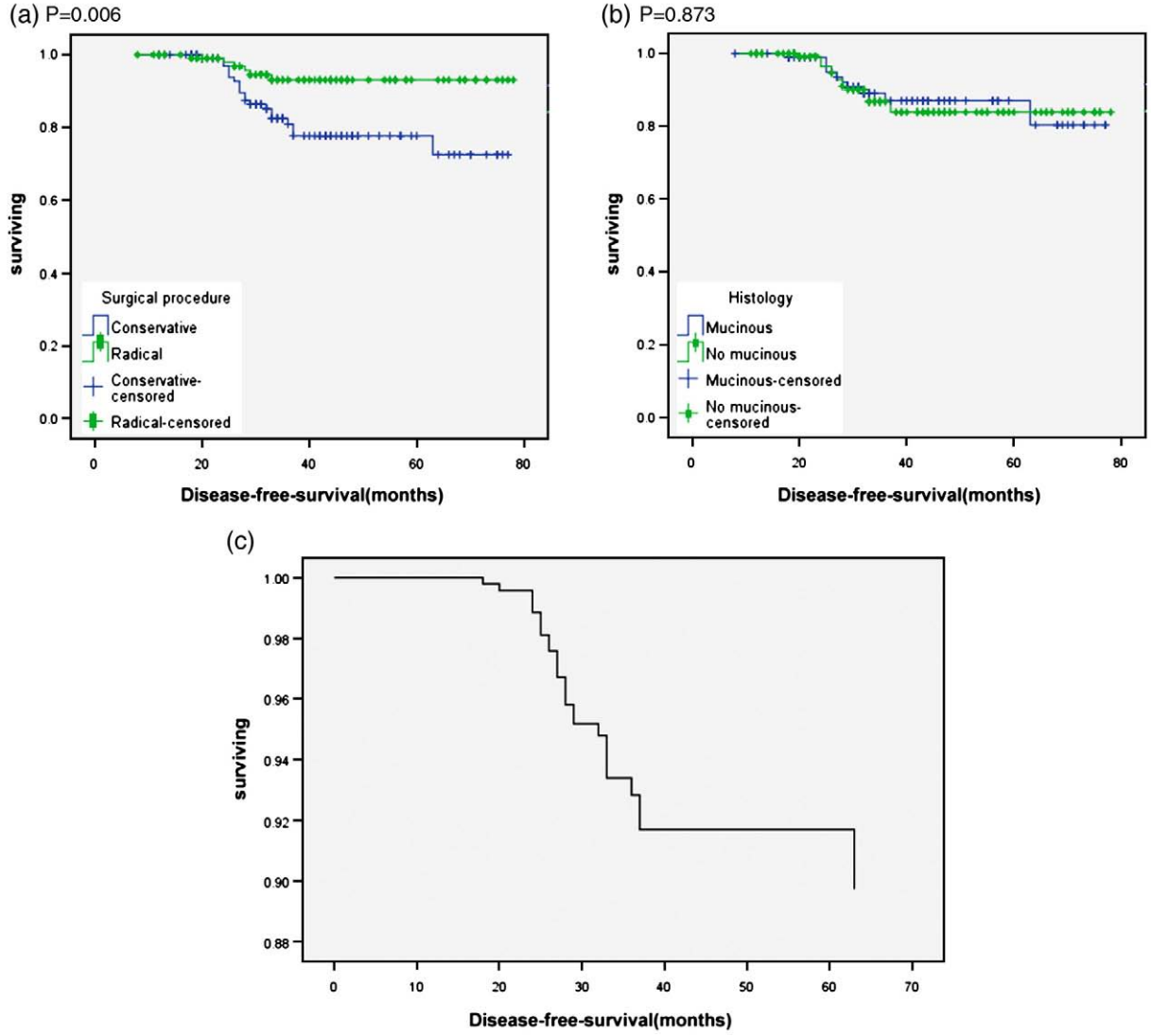

Fig. 2. Disease-free-survival rates according to: (a) surgical procedure; (b) histology. Statistical differences of univariate Kaplan±Meier curves were calculated by log-rank comparisons. Overall disease-free-survival curves (c) was performed by the cox proportional hazards model.

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(RR=2.742, $P=0.010$) as significant independent variables related to DFS after curative surgery for BOTs. (Fig. 2c was the overall disease-free-survival curves).

Discussion

Borderline ovarian tumors usually present at earlier stages than invasive tumors. In our study, 69% of the patients were FIGO stage I. Stage III (23%) was more common than stage II disease (8%), and stage IV disease was not encountered. We found the incidence of recurrence was higher among patients with advanced stage disease. Even though CA-125 was not an independent factor for recurrence, it had an association with advanced stage and was elevated at the time of recurrence. It appears that CA-125, as well as CA-199, may have a role in the detection of recurrence in patients with borderline ovarian tumors [7].

Borderline ovarian tumors are frequently diagnosed in women of reproductive age. Approximately one-half of such diagnoses are made in women younger than 40 years of age in our study. The treatment of this tumor, as in malignant ovarian diseases, has traditionally been radical surgery (hysterectomy with bilateral salpingo-oophorectomy) so as to reduce the risk of recurrence. But over the last two decades, because the prognosis is excellent (99% have long-term survival in stage I disease [8]), this dogma has been abandoned in favor of more conservative surgery in order to preserve subsequent fertility in young patients with borderline ovarian tumors. In our conservative surgery group, 20 of 119 patients (16.8%) developed recurrence compared to 6 of 115 (5.2%) in the radical surgery group. The risk of recurrence was increased in cases of conservative surgery. The conservative surgery procedure was a significant factor in disease recurrence and also served as a significant independent predictor related to DFS in our patients.

Most investigators consider that in conservative procedures, prophylactic measures, such as unilateral adnexectomy rather than cystectomy, may reduce the incidence of recurrence. Therefore, cystectomy should be restricted to women with bilateral disease or a unilateral ovary [9]. In accordance with previous studies, the incidence of recurrence in our study was lower among those patients who underwent unilateral adnexectomy as compared to cystectomy ($p<0.01$).

In women with advanced stage disease, if they have undesired fertility, the optimal treatment is total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Complete staging requires pelvic lymph node sampling, with at least palpation. Because the incidence of lymph node invasion is low, the need to stage borderline tumors with lymph node biopsies is still not established [10]. However, appendectomy should be classically added to the staging, particularly when mucinous tumors are involved.

Laparoscopy has become an alternative for the treatment of women with borderline ovarian tumors. Such an approach improves the immediate postoperative quality of life by reducing adhesions. The main concerns regarding laparoscopic treatment of borderline ovarian tumors include the risk of inadequate initial staging, tumor cell dissemination, and recurrence. In the present study, laparoscopy was more frequently preformed in younger and infertile women. Although the recurrences we observed were probably unrelated to the approach itself (laparotomy or laparoscopy), radical or staging surgery was not performed in the laparoscopy group; large tumor size appeared to be a limitation for laparoscopy and an indication for laparotomy. Rupture of the cyst occurred more frequently in the laparoscopic group, which might increase the likelihood of peritoneal implants. Based on the results of our multivariate analysis, both rupture of the cyst and peritoneal implants were independent prognostic variables. To obtain the most effective results in case of borderline ovarian tumors, laparoscopy should be reserved for the treatment of small-volume tumors and performed by well-trained gynecologic oncologists following strict criteria [4].

With respect to the use of postoperative chemotherapy, in our study population, the incidence of recurrence was not different when the women who received chemotherapy were compared with those who were not treated ($p=0.856$). This observation seems to confirm the results of prospective studies performed by other authors [11]. However, Sevcik [12] has also recommended that patients presenting with risk factors, such as advanced stage tumors, bilateral ovarian tumors, positive peritoneal cytology, tumor rupture, and high-risk histologic features, should be administered postoperative chemotherapy.

To date, no consensus exists on the size criteria for microinvasive lesions or the inclusion of other factors, such as stromal reaction or degree of cellular atypia. Most investigators believe that microinvasion, regardless of the histologic subtype of the tumor, does not change the patient's overall prognosis [13,14]. Nevertheless, Buttin [15] has suggested a possible association between microinvasion with higher recurrence rates and worse prognosis. The combination of microinvasion and advanced stage has also been proposed as an adverse prognostic factor. Similarly, our study showed that 5 of 13 (39%) borderline ovarian tumors with a microinvasive architecture recurred compared with 21/221 (10%) borderline ovarian tumors without a microinvasive architecture. Multivariate analysis demonstrated that microinvasion is a factor associated with recurrence and poorer DFS.

A micropapillary pattern was present in 20% of the serous borderline tumors in our data. A micropapillary pattern has a higher frequency of bilaterality, surface ovarian involvement, advanced stage, stromal microinvasive foci, and invasive implants; the presence of a micropapillary pattern thus translates into higher recurrence rates and lower survival among patients [16]. It is interesting that, in our study, micropapillary architecture was associated with recurrence by univariate analysis, but was not an independent adverse prognostic feature by multivariate analysis. This may due to short duration of follow-up in our series. We strongly believe that this group of patients merits further investigation, particularly with regard to possible recurrence.

Conclusion

Although borderline ovarian tumors have an excellent prognosis, they are not exempt from the risk of recurrence.

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Identification of patients with high-risk factors is essential in order to prevent their recurrence. Regular follow-up is needed for early detection and management of recurrence. Given the fact that borderline ovarian tumors can recur after 10 years, it seems reasonable to extend the follow-up interval to 10 years after initial diagnosis[17,18], at least in the high-risk groups of patients, such as those mentioned above.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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