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Borderline ovarian tumours: A single institute retrospective study

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Abstract
Borderline ovarian tumours (BOT) are a group of ovarian epithelial tumours defined by atypical epithelial proliferation without stromal invasion. Recurrence and malignant transformation can occur. Our aim was to determine the clinical, epidemiologic and histological features of the BOT by a retrospective *coorte* study involving 79 patients diagnosed with BOT and treated at IPO-Coimbra Between 1990-2016. After a mean follow up of 5, 9 years, we reported 4 cases of relapse, 3 with malignant transformation to invasive ovarian cancer. The overall survival at 5 and 10 years was respectively of 100% and 96, 2%. Ca125, FIGO stage and extra-ovarian peritoneal implants were associated to disease recurrence. Neither micropapillary growth pattern nor age showed that association. It is essential to standardize the clinical practice in different hospitals.

Keywords: borderline ovarian tumours; risk of relapse; overall survival

Introduction

Borderline tumours of the ovary (BOT) are a specific group of epithelial ovarian malignancies, histologically defined as a heterogeneous group of lesions with atypical epithelial proliferation without stromal invasion [1, 2]. They represent 10-20% of epithelial ovarian neoplasms with an incidence of 1, 8-4, 8/100.000 women per year. Typically, they have a good prognosis, compared to invasive ovarian cancers (5 and 20-year survival rate of 97% and 89%, respectively) [2]. They are more frequent in pre-menopausal women, which emphasizes the importance of fertility sparing surgery in patients who want to preserve their childbearing potential [3]. 15 to 40% of BOTs are associated with peritoneal implants. Invasive peritoneal implants are thought to have direct adverse influence toward relapse. However, studies have indicated that tumours with non-invasive implants also resulted in 30% of relapse rate or progressive disease [4]. Complete staging is currently the standard surgery treatment for BOT patients [2, 5]. But the manner and extent of management of these patients are not clear yet. Ovarian borderline tumours remain a controversial issue, in respect to surgical procedures, prognostic factors, postoperative treatment in advanced stage disease, role of fertility sparing surgery and follow-up strategies [1, 2, 5, 6, 7].

The aim of this retrospective study was to determine the clinical, epidemiologic and histological features of Borderline tumours of the ovary, as well as to determine the impact of these clinicopathological factors on recurrence and survival of BOT patients.

Materials and Methods

102 patients were diagnosed to have BOT from 1996 to 2016 at Department of Gynaecologic of Instituto Português de Oncologia de Coimbra Francisco Gentil (IPOCFG). The case records of these patients were analysed in detail for demographic profile, clinical features, treatment and outcome. Follow-up information was available for 79 cases. The remaining 23 patients were lost to follow-up. Tumours were graded, staged and classified by the Department of Pathology of IPOCFG according to WHO and FIGO 2018 criteria. The following parameters were registered for each patient: age at primary diagnosis, menopause state, parity status, clinical presentation, histology (histological subtypes, micropapillary architecture and type of extra-ovarian implants), stage by FIGO, pre-operative Ca125 serum level, surgical procedure performed (complete vs. conservative), tumour size, information about adjuvant therapy, time until recurrence and type of recurrence (borderline or invasive).

Complete surgery was defined as abdominal hysterectomy and bilateral salphingo- ophorectomy, infracolic omentectomy and multiple peritoneal biopsies. Conservative surgery was defined as unilateral adnexectomy, or unilateral salpingo-oophorectomy plus contralateral cystectomy or bilateral cystectomy, with infracolic omentectomy and multiple peritoneal biopsies. Appendicectomy was performed in all mucinous tumours as a part of surgical staging. Recurrence was defined by the reappearance of the disease during the follow-up, after histologic confirmation. The group studied the association between the recurrence and these factors: age, pre-operative Ca125 serum level, FIGO stage, micropapillary growth pattern and extra-ovarian peritoneal implants. Overall survival was defined as the time from the date of primary surgery to BOT specific death. The follow-up period was defined by the time between the initial diagnosis and the date of the last medical appointment or death.

The data was analysed with the SPSS version 15.0 statistical programme. Categorical variables were evaluated using the chi-square test. A p-value of less than 0.05 was considered statistically significant. Due to the retrospective nature of

the study, informed consent was waived by the Medical Ethics Committee of the institute.

Results and Discussion

The retrospective *coorte* included 79 patients diagnosed with BOT and treated at IPOCFG between 1990 and January 2016 (Table 1). The average age of presentation was 50, 3 years (range 18-83). 24, 1% of the patients were under 40 years. 38 in 79 patients were premenopausal. The most common presenting symptom was abdominal distension, seen in 24% of patients. 54% of patients were asymptomatic. In these cases, BOT were incidentally detected by ultrasound imaging or intraoperative findings in surgeries performed for other reasons. CA125 serum level was raised (>35 IU/ml) in 46 patients. Only 25% (20) patients had a CA125 value of more than 100 IU/ml. Bilateral ovarian masses were noted in 25% patients (20). The median tumour diameter was 121 millimetres. Serous borderline ovarian tumour was the most common histologic subtype. This retrospective study included 25 mucinous tumours, 48 serous, 2 endometrioid, 3 seromucinous and 1 Brenner tumour. 88,6% of them were in stage I (FIGO), 7,6% in stage II (FIGO) and 3,8% were in stage-III (FIGO). Patients in stage IV (FIGO) were no diagnosed. All patients had surgery as a primary treatment; in 32, 9% of the cases (26) was performed a conservative surgery, and the remaining patients underwent a complete surgical procedure. Extra-ovarian peritoneal implants were noted in 9 cases, 8 of them (6, 3%) where histologically classified as non- invasive peritoneal implants. 2 patients were treated with adjuvant chemotherapy: 1 had invasive peritoneal implants, IIIB FIGO disease. The other patient had non-invasive peritoneal implants, IIB FIGO disease. After a mean follow up of 5, 9 years (range 1-14 years), we reported 4 cases of relapse, 3 with malignant transformation to invasive carcinoma (Table 2). The time to recurrence varied between 3 months and 9 years. Only 1 of these 4 women had been treated with systemic chemotherapy. 3 patients died during the period of follow up: patient number 1 and patient number 2 (Table 2); one patient died due to cardiac complications. The overall survival at 5 and 10 years was respectively of 100% and 97, 5%. Due the fact that we only had 2 deaths related to BOT, it wasn't possible the statistical analyse about the factors that influence the survival. As we see in Table 3, statistical analyses using the chi-square test didn't show association between recurrence and micropapillary growth pattern neither age (p>0,05). On the other hand, we verified association between relapse and the following factors: pre-op Ca125 serum level, FIGO stage and extra-ovarian peritoneal implants (invasive and non-invasive) (p<0, 05). As conclusion, patients with borderline ovarian tumours are younger than those with invasive ovarian carcinoma. 54% of patients were asymptomatic and were diagnosed by pelvic ultrasound or accidentally during a surgery made by another reason. This fact highlights the importance of instituting a sensitive sonographic screening for the adnexal masses [8]. Almost half of the patient was pre-menopausal, although only 33% of the women had performed a conservative surgery. The discussion about the type of surgery (conservative vs complete) should be made in every pre-op appointment; all women should be conscious for the similar recurrence risk between conservative and complete surgery, like previous studies had stated [9, 10]. More than 58% patients had raised CA125 serum level. The most common histologic type was serous BOT, followed by mucinous BOT. Similar incidence has been reported in other studies as well [11, 12]. The majority of patients were diagnosed in FIGO stage I, and none of patients had FIGO stage IV disease, according the overall good prognosis of these tumours [11, 13]. Concerning to systemic treatment, only 2 patients underwent adjuvant chemotherapy: 1 had invasive peritoneal implants, IIIB FIGO disease. The other patient had non-invasive peritoneal implants, IIB FIGO disease. According to the records, there were other patients with FIGO stage ≥ II disease who didn't received any systemic treatment, which emphasizes the importance of clarify the mainly criteria for adjuvant chemotherapy in management of BOT [3, 14]. Besides that, we notice that only 1 of the 4 women who relapsed had been treated with adjuvant systemic chemotherapy. This fact leads us to underline the necessity of identify the factors that impact in the recurrence risk of BOT, in order to choose the patients that would most benefit of the adjuvant treatment or more regular surveillance [2, 15, 16, 17]. In this group, serous BOT was the most common histological type in women with recurrence. Concerning to histologic type, the literature is not clear: the mucinous histological type has been reported to be associated with a worse prognosis in comparison with serous BOTs [7] but the opposite was also seen [2]. Our univariate statistical analysis showed that Ca125 serum level, FIGO stage and extra- ovarian peritoneal implants are factors related to disease recurrence. In our retrospective study, neither micropapillary growth pattern nor age showed that association (p>0, 05). In the group of relapses, only 1 patient had FIGO stage I disease; all of them had elevated Ca125 serum level and half of them had extra-ovarian implants. Even though the small size of our *coorte*, we can summarize that there are clinicopathological factors related to the probability of recurrence, as other studies had already reported [2, 7, 15, 16, 17, 18]. The overall survival at 5 and 10-years was respectively of 100% and 97, 5%. The 2 women dead had recurrence of the disease in form of invasive carcinoma. Other woman with invasive recurrence is still alive. Our study shows a 10-years survival rate about 33% in women with invasive carcinoma recurrence, but our coorte is very small to take important conclusions.

Tables and Figures

Table 1: Clinical and Histopathological Features and Outcomes

Total number of patients	**79 (100%)**
Clinical presentation	
Increased abdominal volume	19 (24%)
Abdominal pain	12 (15%)
Irregular bleeding	5 (7%)

Asymptomatic	43 (54%)
Parity	
Nullipara	12 (15%)
Primipara	21 (27%)
Multipara	46 (58%)
Menopausal state	
Pre	38 (48%)
Post	41 (52%)
Ca125>35IU/ml	46 (58%)
Bilateral masses	20 (25%)
Tumour size (medium)	121 millimetres
Serous	48 (61%)
Mucinous	25 (32%)
Endometrioid	2 (2, 5%)
FIGO Stage	
I	70 (88, 6%)
II	6 (7, 6%)
III	3 (3, 8%)
Surgery	
Conservative	26 (33%)
Complete	53 (67%)
Chemotherapy	2
Recurrence	4

Table 2: Patients who recurred.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Age	38	67	35	59
FIGO Stage	IB	IA	IIIB	IIIB
Histology of Primary tumour	Serous BOT	Mucinous BOT	Serous BOT	Serous BOT
Ca 125 (IU/ml)	184,2	352	2297	436,6
Peritoneal implants	No	No	Yes (non-invasive)	Yes (non-invasive)
Type of surgery	Complete	Complete	Conservative	Complete
Micropapillary growth pattern	Unknow	No	Unknow	Unknow
Time to relapse	7 years	9 years	3 months	8 years
Type of recurrence	Invasive disease	Invasive disease	Invasive disease	Borderline disease
Local/form of recurrence	Pelvic mass	Pulmonary nodules	Contralateral ovary	Pelvic carcinomatosis

Table 3: Bivariate analyses using chi-square test.

(p-value < 0.05 was considered statistically significant)		
	p-value	**Association with disease recurrence**
Age	0,85	No
FIGO Stage	<0,05	Yes
Ca 125 (IU/ml)	<0,05	Yes
Peritoneal implants	<0,05	Yes
Micropapillary Growth Pattern	0,25	No

Conclusions

We conducted a study about the clinical, epidemiologic and histological features of Borderline tumours of the ovary, as well as the impact of these clinicopathological factors on recurrence and survival of BOT patients. Our study has weaknesses: the size of our coorte, the women lost during the follow-up, the retrospective character of it and the multiplicity of surgical approaches (some of these women underwent surgery outside the institution). Beyond the weaknesses, we can conclude that BOT behaves much better in prognosis than invasive ovarian cancer. The potential for relapse and death in the long-term follow-up is determined by multiple factors, and the most important are: Ca125 serum level, FIGO stage and the presence of peritoneal implants. So, in our opinion, it is mandatory to check all these factors in pre- and post-operative appointment and to discuss the possibility of chemotherapy in elevated risk patients. It is essential to standardize the clinical practice in different hospitals. In conclusion, prospective evaluations with systematic assessment of all disease- related characteristics are warranted for a better understanding and a conclusive evaluation of the biological behaviour of BOT.

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