Borderline tumors of the ovary

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Tumeurs borderlines de l'ovaire

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R É S U M É

Pré-requis : Les tumeurs borderline de l'ovaire (BOT) ont été décrites pour la première fois par Taylor en 1929. Ces lésions ont un pronostic plus favorable que celui des autres cancers de l'ovaire. Leurs pronostic et traitement font encore l'objet de discussion puisqu'elles surviennent le plus souvent chez des jeunes femmes où la chirurgie conservatrice de la fertilité est toujours considérée en premier.

But: Evaluer le traitement des patientes avec tumeur à la limite de la malignité de l'ovaire.

Méthodes: Il s'agit d'une étude rétrospective à propos de 40 patientes ayant des tumeurs à la limite de la malignité de l'ovaire traitées entre le 1er janvier 1991 et 31 Décembre 2004.

Résultats: Le suivi médian était de 43 mois, l'âge moyen était de 44 ans. La chirurgie initiale était conservatrice chez 17 patientes et radicale dans 23 cas. Six patientes avaient une maladie résiduelle. Les tumeurs séreuses, mucineuses et mixtes étaient observées dans 18, 21 et 1 cas respectivement.

Les stades I, II, III ont été observés dans 26, 5 et 9 cas respectivement avec deux cas de pseudomyxomes. La chimiothérapie adjuvante était administrée chez 3 patientes. La récidive était notée chez 13 patientes et sept sont décédées. La survie globale à 5 ans était de 78%. Les facteurs de mauvais pronostic étaient l'âge, le type de chirurgie et la maladie résiduelle. Avec le model de Cox, l'analyse multivariée a isolé la maladie résiduelle comme facteur indépendant de la survie globale, d'autre part l'âge et le type de chirurgie étaient significatifs pour la survie sans récidive.

Conclusion: Une stadification attentive suivie d'une chirurgie radicale est obligatoire. L'annexectomie unilatérale avec omentectomie, biopsies péritonéales multiples et cytologie péritonéale peuvent être indiquées chez des patients en âge de procréer. La chirurgie radicale après la grossesse est conseillée.

M o t s - c l é s

Ovaire, tumeur, borderline, pronostic, traitement.

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S U M M A R Y

Background: Borderline tumors of the ovary (BOT) were described for the first time by Taylor in 1929. These lesions have a more favorable outcome than do other ovarian cancers. Their prognosis and treatment are still subject of discussion since they occurred more often in young women where the sparing fertility surgery is always considered primarily.

Aim: Evaluate the management of patients with borderline ovarian tumors.

Methods: A retrospective study was conducted in 40 patients with borderline ovarian tumors treated between January 1, 1991 and December 31, 2004.

Results: Median follow-up was 43 months, mean age was 44 years. Initial surgery was conservative in 17 patients and radical in 23 cases. Six patients had residual disease. Serous, mucinous and mixte tumors were observed in 18, 21 and 1 cases respectively.

Staging was I, II, III in 26, 5, and 9 cases respectively with two pseudomyxomas. Adjuvant Chemotherapy was given in 3 patients. There was a recurrence in 13 patients and seven died. The 5-year overall survival rate was 78 %. Prognostic factors with an impact on survival rate were age, stage of the disease, histological subtype and residual tumor. Factors with a negative impact on recurrence were age, type of surgery and residual disease. With Cox multivariate analysis, residual tumor is an independent factor for overall survival, on the other hand age and type of surgery were significant for recurrence free survival.

Conclusion: Careful staging followed by complete and radical surgery is mandatory. Unilateral salpingo-oophorectomy with omentectomy and multiple peritoneal biopsies and washing could be indicated in patients with child bearing age. Radical surgery after pregnancy is advised.

K e y - w o r d s

Ovary, Tumor, Borderline, prognosis, treatment.

Taylor first described low malignant potential ovarian tumours (LMPOT) in 1929 [1]. This ovarian malignancy is defined by an epithelial tumour with a stratification of the epithelial lining, but with a lack of frank stromal invasion at pathologic examination. It has a less aggressive behaviour than invasive epithelial ovarian tumours. The prognosis of patients with a disease limited to the ovary is excellent, but patients with extra-ovarian spread have an uncertain prognosis and evolution. The evolution of patients with advanced stage of borderline ovarian tumors (BOT) depends on the histological subtype. Recent series reported that 30% of patients with serous borderline tumours with peritoneal implants had recurrences, most commonly in the form of serous carcinoma.

This study aims at determining the prognosis and clinicopathologic characteristics of patients with BOT.

PATIENTS AND METHODS

Patients

From January 1991 to December 2004, data from 40 patients treated in the Institut Salah Azaiz of Tunis, for BOT were reviewed.

Inclusion criteria: Histological criteria to characterize ovarian tumors and peritoneal implants have been previously reported [2]. Peritoneal implants were classified as either non-invasive or invasive, according to the absence or presence of stromal invasion of the peritoneum, respectively. The staging used was the 1987 International Federation of Gynaecology and Obstetrics (FIGO) classification [3].

Preoperative assessment

Patients underwent preoperative ultrasonography. A CA 125 level > 35 UI/ml was considered as positive before the surgical procedures.

Treatment

Radical treatment was defined as bilateral salpingo-oophorectomy (BSO) with or without hysterectomy. Conservative treatment was defined as a surgical procedure with conservation of the uterus and at least a portion of one ovary. Therefore, four possible types of conservative surgical procedure could be performed: unilateral adnexectomy (UA); UA plus contralateral cystectomy (UA+CC); unilateral cystectomy (UC); and bilateral cystectomy (BC).

It was possible that additional surgical procedures were performed: peritoneal washings, biopsy of the remaining ovary, omentectomy, appendicectomy, multiple peritoneal biopsies and pelvic and/or para-aortic lymphadenectomy. The performance of some of these surgical procedures depended on the date at which treatment was given, the surgeon preferences and the diagnosis of BOT during or after the surgical procedure. Complete and accurate surgical staging included peritoneal cytology and omentectomy with or without systematic multiple peritoneal biopsies.

Follow-up and outcome

Follow-up of patients included clinical examination, blood tests (CA 125 and eventually CA 19.9 levels) and an abdominopelvic ultrasonography every 3 months during the first year following the procedure, then every 6 months for 2 years, and finally annually.

For the statistical analysis, the following characteristics were studied: stage, type of surgery, persistence of residual tumour, nodal status, characteristics of peritoneal implants (non-invasive or invasive). Roc curve was used to determine the statistical cut-offs of numeric variables. Pearson Chi squared and exact fisher test were used to investigate any correlations between different variables. Overall survival rates were determined by using the Kaplan–Meier method and 95% confidence intervals were calculated by the Rothman method [8]. The log-rank test was used to compare the curves and to determine the P value. A P value of <0.05 was considered as significant.

RESULTS

The median age of the 40 patients at the time of surgical procedure was 44 years (range 15–76). Forty five percent of patients were aged less than 40 year-old. Preoperative CA 125 levels were available in 21 patients. Fourteen of them had CA 125 levels > 35 U/l with a mean level of 98 ± 129 U/l. Sixty five per cent of the patients had stage I disease and 22.5% had stage III disease. The correlation between the stage and histological type concluded to higher frequency of mucinous tumors in stage III of the disease. Five patients had non-invasive implants and three had invasive implants.

Seventeen patients underwent conservative surgery. Thirteen patients of them were aged 40 year-old or less. The clinico-pathologic characteristics of these patients are given in Table 1. Adjuvant chemotherapy based on Endoxan and platinum was given in two patients with invasive implants and 5-fluorouracil in one patient with mucinous ovarian tumor. Abdomino-pelvic external radiation therapy was delivered to one patient.

At the end of initial surgery, three patients had absence of residual disease, three had a residual tumour 2 cm and two a residual tumour >2 cm Table 2.

Thirteen (32,5%) patients had recurrences. All these patients had abnormal clinical examination, CA 125 levels or ultrasound examination, and underwent an iterative surgical procedure with histological confirmation of their recurrent disease. The median delay for recurrences was 4.5 years (range 3 months–22 years). Nine patients relapsed with the same borderline histology treated previously (with iterative conservative treatment in three patients). Eight patients (61.5%) were found with mucinous type, and five (38.5) with serous type. Eight patients (61.5%) were found with stage I, two (15.4%) with stage II and three (23.1%) with stage III. The initial mean tumor size of the recurrent diseases was 22 cm with 62% of the tumours had a size more than 18 cm. In seven cases the recurrence was located in the pelvis and in six cases in the peritoneal cavity. All the recurrent tumors occurred under the

form of borderline tumour. The 5-year recurrence free survival (RFS) of the patients treated conservatively and radically were 32% and 70%, respectively (P = 0.03). Other studied factors are shown in Table 3. With the use of Cox regression model only the type of surgery and age remained independent prognostic factors for recurrence free survival.

Table 1: Clinicopathologic characteristics of the patients with borderline ovarian tumor

Number of patients	Percentage	(%)
Age		
15-24	5	12.5
25-34	11	27.5
40-44	4	10
45-54	7	17.5
55-64	8	20
65-76	5	12.5
Revealing symptoms		
Pelvic pain	22	55
Increase of abdominal perimeter	22	55
Pelvic mass	12	30
Metrorrhagia	5	12.5
Fortuitous	4	10
Frozen section analysis		
Not performed	9	22.5
BOT	21	52.5
Benign tumor	9	22.5
Ovarian cancer	1	2.5
Histological type		
Mucinous	21	52
Serous	18	45
Mixed	1	2.5
Type of implants		
Non invasive	5	62.5
Invasive	3	37.5
Stage FIGO		
Stage Ia	18	45
Stage Ib	4	10
Stage Ic	4	10
Stage IIb	2	5
Stage IIc	3	7.5
Stage IIIa	4	10
Stage IIIb	1	2.5
Stage IIIc	4	10
Total	79	100

BOT: Borderline ovarian tumor

Seven (17,5%) patients died of tumour progression within a mean period of 80 months (ranging from 5-300 months) following the date of the initial surgery. Among these patients, three underwent adnexectomy and four total hysterectomy with bilateral salpingo-ophorectomy. In six cases the tumors were mucinous and serous in one case. In three cases the tumors were satged IIIc and in four cases stage I.

With a follow-up time that ranged from 1 to 300 months (mean, 43 months), the 5 year overall survival was 78%. With the use of log-rank for univariate analysis, the age, the presence of residual tumor and the histological subtype of the tumors were prognostic factors for overall survival. Other studied factors did not reach the statistical significance Tables III. With the use of the Cox regression model, only the presence of residual tumor remained significant independent predictor for survival.

Table 2: Therapeutic modalities

	No. of Patients	%
Surgical Procedure		
Radical	23	57.5
Conservative	17	42.5
Residual tumor		
No	34	75
Yes	6	15
< 2 cm	2	5
> 2 cm	4	10
Adjuvant treatment		
No	36	90
Yes	4	10
CT	3	7.5
RT	1	2.5

*: Patients received concomitant chemotherapy

DISCUSSION

The BOT represent 10 à 15 % of ovarian malignant tumors [4]. In our series, BOT represent 10% of all ovarian cancers treated in our center in the same period. Their incidence in North European countries and North America is 1.6 to 4.8 /100.000 patients [5]. The incidence rises with the age until 45-49 years then it stabilizes.

The mean age of BOT patients vary from 35 to 52 years, so 10 years younger than that of invasive ovarian tumors [4, 6-8]. In our series the mean age of our patients is 44 years.

Several epidemiologic studies showed similar risk factors with invasive ovarian tumors [9, 10]. Sykes and Casey showed in their series 47 % and 44 % of nulliparous women [11]. In our series, 32% of our patients are nulliparous. The young age is reported as a risk factor for BOT, in teenagers, there are 30% of BOT in contrast to 6 % to 10 % of invasive ovarian tumors. Besides, in patients younger than 40 year old, at least 50% of ovarian tumors are BOT. In our series 45% of our patients are aged 40 year old or less.

The prognosis of BOT is better than that of invasive ovarian carcinomas. Several prognostic factors were discussed in the literature, the first one being the stage of the disease. In the series by Bell [12], 4% and 20% of stage II and III patients, respectively, died of tumour. In the series by Manchul [13], the

Table 3: The 5-year disease-specific survival of treated patients with borderline ovarian tumor related to several clinicopathological variables

Factor	5-year overall survival(%)	P value univariate free survival	5-year recurrence (%) univariate	P value
Stage		0.017		ns
I (26)	86.5%		66%	
II (5)	64%		50%	
III (9)	29%		34%	
Type of surgery		ns		0.03
Conservative (17)	74%		32%	
Radical (23)	79%		70%	
Age		0.004		0.0004
< 60(30)	86 %		68%	
> 60(7)	41 %		21%	
Residual tumor		<10-4		0.04
No (34)	88%		60%	
Yes (6)	33%		33%	
Histological subtype		0.01		ns
Mucinous (21)	64%		50%	
Serous (18)	100%		58%	
Peritoneal implant		ns		ns
Yes (8)	100%		32%	
No (32)	74%		60%	
Recurrence		ns		-
Yes (13)	62%			
No (27)	95%			

10-year survival rates were, respectively, 75% and 50% in patients with stage II and III disease. In the series by Leake [14], the rates of recurrence were, respectively, 54% and 17% in patients with stage III and II disease. In Michael and Roth's study [15], the prognostic significance of disease stage was much greater than other factors. For Koern [16], the tumor stage was the most relevant prognostic factor of BOT. In our study, the stage of the disease was significant for overall survival but not for recurrence free survival.

Another clinical factor that was examined was the existence of residual tumour at the end of surgery. In several series, persistence of residual disease is an independent prognostic factor [17-20]. In our series this factor was the only independent prognostic factor for the overall survival. We conclude that the surgical procedure for borderline tumours with peritoneal disease, as in invasive ovarian tumor, should include a resection of all macroscopic peritoneal implants. Optimal surgery is mandatory to obtain complete removal of all peritoneal tumour. Thus, we may obtain a correct pathological diagnosis based on the entire tumour tissue.

Previous studies debated the role of histological subtypes of peritoneal implants (invasive or non-invasive ones) as a prognostic factor [21, 22]. The most recent studies are those published by Gershenson [23, 24], showed in a large series that the rate of recurrence observed in patients with invasive and non-invasive peritoneal implants was similar. Most of them recurred with evolutive invasive disease. In our series, the presence of peritoneal implants was not significant for overall or recurrence free survivals and all recurrent tumors were under the form of BOT. In contrast, Morice [25] shows that the rate of evolutive invasive disease is significantly different in patients with invasive peritoneal implants compared to patients with non-invasive implants (31% versus 2%; P <0.002). Other reports suggest a very good survival in patients with peritoneal implants with 10-year survival of 95% [14, 26-28].

The micropapillary pattern of some BOT is also a prognostic factor that has been studied to explain the poor prognosis of a subgroup of patients with non-invasive peritoneal implants [29, 30]. Micropapillary pattern was more commonly associated with invasive than non-invasive implants [29, 30]. The 10-year actuarial survival rates of patients with non-invasive implants, invasive implants or MPSC were 98%, 33% and 71%, respectively [29]. This histological pattern was not studied in the present study.

Stromal micro-invasion was also discussed as a prognostic factor in a series of Buttin [31]. Nevertheless, in other series, like in our study, presence of stromal microinvasion is not an adverse prognostic factor [25, 29].

The place of conservative treatment in the surgical management of BOT is another important issue. Several series have studied the results of conservative treatment in early stages of the disease. The rate of ovarian recurrence following conservative treatment is higher than in patients undergoing a radical treatment [32, 33]. This rate is even higher following cystectomy [17, 18, 26, 34]. We have found that the type of surgery (conservative or radical) is not a prognostic factor for overall survival but was associated with higher recurrence rate. All patients who recurred following conservative treatment had recurrence under the form of borderline tumour.

Such recurrence was easily treated with a new conservative surgical approach [35]. Initial radical surgery would probably not change the evolution of these two patients. Thus, performing conservative surgery did not affect survival.

In our study, the type of surgery (conservative or radical) did not affect the overall survival as well as for the occurrence of tumor recurrence. In patients with invasive implants, we prefer to perform a radical surgery.

The initial treatment of patients with peritoneal implants is mainly surgical and includes removal of all macroscopic disease with appropriate surgical staging (including omentectomy).

Adjuvant therapy on peritoneal implants of borderline tumours remains controversial. Barakat [36] report responses following chemotherapy in patients with advanced stage borderline tumour of the ovary. On the other hand Kaern [37] observed that adjuvant chemotherapy does not improve survival. In the present series, only three patients with invasive implants had adjuvant Platinum based chemotherapy. This underlines the need for treatment to be based on optimal surgery with removal of all macroscopic disease. In patients with non-invasive implants, this surgical procedure should be the exclusive therapy [4].

CONCLUSION

BOT are uncommon but not rare neoplasms; most are of serous or mucinous type. Their diagnosis is difficult needing an experienced pathologist for extemporaneous exam. Their prognosis remains better than that of the epithelial ovarian tumors. Many prognostic factors are identified. In the present series the most important prognostic factor for patients with BOT is the presence of residual tumor after initial surgery. Since BOT occur in young women, conservative management must be considered as first line treatment in patients of child-bearing age. The treatment of patients with advanced stage borderline tumour is based on optimal surgery and should include removal of all macroscopic disease. Adjuvant chemotherapy could be discussed in patients with invasive implants

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