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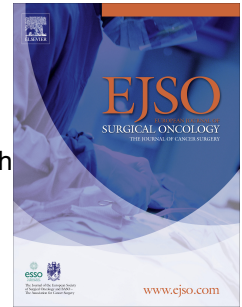


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**IMPACT OF SERUM TUMOR MARKER DETERMINATION ON THE
MANAGEMENT OF WOMEN WITH BORDERLINE OVARIAN TUMORS:
MULTIVARIATE ANALYSIS OF A FRENCH MULTICENTRE STUDY.**

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Preoperative evaluation of serum tumor markers impacts on the management of borderline ovarian tumors.

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**Impact of serum tumor marker determination on the management of women with
borderline ovarian tumors: multivariate analysis of a French multicentre study.**

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ABSTRACT:

Objective: To evaluate the contribution of preoperative serum tumor markers to manage borderline ovarian tumors (BOT).

Study Design: Retrospective multicentre study including 317 BOT. Serum tumor marker levels of CA125, CA19-9, CEA, and CA15-3 were determined by radio-immunoassay.

Results: Among 181 women with serous BOT and 136 women with mucinous BOT, respectively 55 of 114 (48.2%) and 38 of 91 (41.8%) had at least one abnormal value. Women with preoperative tumor marker assays were more likely to have radical treatment ($p=0.0001$), full staging ($p=0.004$), and intraoperative histology ($p<0.0001$). Women with at least one abnormal tumor marker were more likely to undergo laparotomy ($p=0.007$), to have intraoperative histology ($p=0.04$) and complete staging ($p=0.0008$). In multivariate analysis, first-line laparoscopy was associated with abnormal tumor marker levels ($OR= 9.63$; $95\%CI=1.40-66.39$; $p=0.02$), while laparotomy was associated with large tumors, bilateral tumors, and ascitis visible on sonography.

Conclusion: Serum tumor marker assays modified both preoperative assessment and surgical management of BOT.

Key words: borderline ovarian tumors, CA125, CEA, CA15-3, CA19-9, tumor markers.

INTRODUCTION

Accepted as a distinct histological entity by the International Federation of Gynecology and Obstetrics (1) and the World Health Organization (WHO) (2) in the early 1970s, borderline ovarian tumors account for 10% to 20% of ovarian epithelial tumours (3). Guidelines for surgical treatment are similar to those for ovarian cancer (4-5). However, one third of borderline ovarian tumors are diagnosed in women younger than 40 years, and more than 80% of cases are detected early in the disease course, raising issues of fertility-sparing surgery, laparoscopic management, and restaging operations (6-15).

Diagnosis of adnexal masses is mainly based on imaging techniques and preoperative serum tumor marker assays (16-21). Serum tumor markers have been evaluated in only small series of women with BOT, and their contribution to treatment and follow-up is unclear (22-24).

Elevated serum tumor markers such as CA125, CEA and CA19-9 have been reported in only 25% to 60% of women with BOT (18, 23-25).

The aims of this retrospective study were to evaluate the contribution of the serum tumor markers CA125, CA19-9, CEA and CA15.3 to the initial management of women with BOT, and to determine their value for detecting recurrences.

MATERIAL AND METHODS

MATERIAL

From January to December 2001 we conducted a retrospective multicenter study of 360 women treated for BOT between 1990 and 2000 in 13 specialized gynecology units and one cancer center. Women with endometrioid (four cases), Brenner (2 cases) and mixed BOT (32 cases) were excluded from the study. The study population thus comprised 322 patients with serous or mucinous BOT. Data were obtained from hospital records, physicians, and direct contact with the patients. All the charts were thoroughly reviewed on site by one of the authors (RF). Ethical review board approval was obtained for the study.

The histological type was established by reviewing hematoxylin/eosin-stained slides, as recommended by FIGO (4). The following histological criteria were used to identify borderline tumors: (a) stratification of the epithelial lining of the papillae, with microscopic papillary projections or tufts arising from the epithelial lining of the papillae, (b) nuclear atypia, (c) mitotic activity, (d) intracystic clusters of free-floating cells, and (e) absence of stromal invasion. Microinvasion and micropapillary features were also recorded.

METHODS

Surgical treatment was considered conservative when at least one ovary and the uterus were spared. Conservative treatment consisted of unilateral cystectomy (UC) or unilateral salpingo-oophorectomy (USO), as well as bilateral cystectomy (BC) and USO + contralateral UC (USO+UC). Initial surgery was considered to be a complete staging operation when all peritoneal surfaces were carefully inspected and peritoneal washing, multiple random or oriented biopsies, and infra-colonic omentectomy were performed. Appendectomy was also a criterion for complete staging of mucinous borderline tumors. Initial surgery was considered an incomplete staging operation in all other cases, independently of the radical or

conservative nature of treatment. The disease was staged as recommended by the International Federation of Gynecology and Obstetrics (4).

SERUM TUMOR MARKERS

Serum levels of CA-125, CA-19.9, CEA and CA-15.3 were measured with radioimmunoassays. Values were considered elevated when CA-125 > 35 IU, CA-19.9 > 40 IU, CEA > 5 IU and CA-15.3 > 30 IU/ml. Serum tumor marker levels in a given patient were considered abnormal if at least one of the markers was elevated.

Five of the 322 women had preoperative serum tumor marker assays that were not mentioned in the charts, and these women were excluded from the statistical analysis.

STATISTICAL ANALYSIS

Univariate analysis was used to compare epidemiological and surgical data between patients with and without preoperative serum tumor marker assays in the entire study population. Then, in the population of women who had preoperative serum tumor marker assays, univariate analysis was used to compare epidemiological and surgical data in patients with normal and abnormal marker status. The chi-square test and Student's t test were used to compare non continuous and continuous variables in univariate analysis.

Multivariate analysis was used to determine the diagnostic and prognostic relevance of preoperative serum tumor markers, and their contribution to detecting recurrences. The primary endpoint in the multivariate model was recurrence. Preoperative pelvic CT, first-line laparoscopic management, and the use of intra-operative histology were secondary endpoints. Associations between clinical, sonographic and serum tumor marker parameters (CA-125, CA-19.9, CEA, CA-15.3) and the above endpoints were identified by multivariable logistic regression analysis. When serum markers were assayed, an additional analysis included the marker level as a binary variable (normal or abnormal).

Correlations between parameters were studied to prevent the selection of strongly correlated parameters in the logistic model. As age and menopause were strongly correlated (correlation coefficient 0.77, $p < 10^{-4}$), we decided to consider age alone and to exclude menopause from further multivariate analyses. Odds ratios (OR) and 95% confidence intervals (CI), as well as p -values, were calculated for both dichotomous and continuous variables.

Backwards elimination was used to select prognostic factors for the different endpoints. It started with a model that contained all explanatory variables identified by univariate analysis. This algorithm eliminated non significant variables and refitted the model repeatedly. This analysis used a significance level of 0.2 to retain variables in the model. To minimize erroneous exclusion of serum markers which could be of prognostic relevance, these markers were forced into the models.

To measure the association between predicted probabilities and observed responses, the reliability of the models was studied with Somer's test statistic. The convergence criterion was satisfied in all models. All significance tests were two-tailed and p values < 0.05 were considered significant. SAS software version 8.2 was used for all statistical analyses.

RESULTS

Study population, and distribution of FIGO stage, type of surgery and biomarkers serum levels according to histological subtype

Among the 317 women included in this analysis, respectively 181 and 136 women had serous and mucinous BOT. Among the women with serous and mucinous tumors, respectively 114 and 91 women had preoperative serum tumor marker assays, of whom respectively 55 and 38 had at least one abnormal result. Details are given in Table 1. In the group of serous tumors, 82 had laparoscopy, with laparoconversion in 21 cases, and 99 laparotomy and the distribution according to FIGO stage was Ia, Ib, Ic, II, III, and IV in 114, 28, 18, 8, 12, and 1 patients, respectively. In the group of mucinous tumors, 49 had laparoscopy, with laparoconversion in 9 cases, and 87 laparotomy and the distribution according to FIGO stage was Ia, Ib, Ic, II, III, and IV in 122, 3, 3, 1, 6, and 1 patients, respectively. In the group of serous tumors, the distribution of abnormal biomarkers according to FIGO stage Ia, Ib, Ic, II, III, and IV was 25, 9, 5, 4, 4, and 1 patients, respectively. In the group of mucinous tumors, the distribution of abnormal biomarkers according to FIGO stage Ia, Ib, Ic, II, III, and IV was 30, 1, 2, 0, 3, and 1 patients, respectively.

Epidemiological and surgical characteristics of women with and without preoperative serum tumor marker assays (Table 2).

Two hundred and five of the 317 women had preoperative serum tumor marker assays. Women with preoperative serum tumor marker assays were older ($p=0.001$), had higher parity ($p=0.03$) and were more likely to be menopausal ($p=0.02$). In addition, these women were more likely to have CT scan ($p<0.0001$) and/or MRI ($p=0.03$) before surgery.

Whatever the results of preoperative serum tumor marker assays, women who had these tests were more likely to have radical treatment ($p=0.0001$) and full staging ($p=0.004$), including peritoneal washing ($p<0.0001$) and random peritoneal biopsies ($p<0.0001$).

Intraoperative histology was more frequent among women who had preoperative serum tumour marker assays ($p<0.0001$). Recurrences were more frequent in women without preoperative tumour marker assays ($p=0.03$).

The women who did and did not have preoperative serum tumor marker assays did not differ with respect to their familial history of cancer, number of pregnancy, presenting symptoms, tumor size on sonography, or the use of first-line laparoscopy, exclusively laparoscopic surgery, optimal cytoreductive surgery, or restaging operation. Mean follow-up among women with and without preoperative tumor marker assays was 34.4 ± 2.6 months and 40 ± 5.1 months, respectively (not significant). Mean disease-free survival was similar in the two groups.

Impact of preoperative serum tumor marker assays on BOT management

Ninety-three of the 205 women with preoperative serum tumor marker assays had at least one abnormal result, and were thus considered to have abnormal serum tumor marker status (Table 3). These women were more likely to have large tumors ($p=0.001$), bilateral tumors ($p=0.01$) and ascitis ($p=0.008$). Using multivariate analysis, First line laparoscopy was more frequent in women with abnormal serum tumor markers ($OR=9.63$; $95\%CI=1.40-66.39$; $p=0.02$). Women with abnormal serum tumor markers were more likely to have intraoperative histology ($p=0.04$) and complete staging ($p=0.0008$) (Table 4).

Women with normal and abnormal tumor markers did not differ in terms of their mean age, familial history of cancer, parity (including nulliparity), menopausal status, presenting symptoms, or the use of preoperative CT scan, first-line laparoscopy and conservative treatment. Likewise, there was no difference in mean follow-up, disease-free survival or the recurrence rate.

Recurrence was more frequent after conservative treatment (OR= 4.44; 95%CI=1.10-18; p=0.04) and in women with FIGO stage > Ia (OR= 7.84; 95%CI=1.73-35.48; p=0.0008). Abnormal serum tumor marker status was not associated with the risk of recurrence (Table 5).

Serum tumor markers during follow-up

Eighty-three women had routine serum tumor marker assays during follow-up, four times during the first year and then twice a year. Six women had abnormal results, of whom four had recurrences and two were recurrence-free, as shown by surgery. Seven women with normal serum tumor marker status during follow-up had recurrences diagnosed on clinical and/or sonographic grounds. The sensitivity, specificity and positive and negative predictive values of abnormal serum tumor marker status for recurrences were 66.6%, 90.1%, 36.4% and 97.2%; and their accuracy was 89.2%.

DISCUSSION

In this large retrospective study, serum tumor marker assays modified the surgical management of women with borderline ovarian tumors. Moreover, serum tumor marker abnormalities during follow-up led to the diagnosis of recurrences.

Low incidence of abnormal serum markers in women with borderline ovarian tumors

Our results confirm the low frequency of serum tumor marker abnormalities in both serous and mucinous BOT, as previously shown in small series. Despite sonographic detection of large or complex ovarian tumors in our patients, and despite their management in specialized centers, less than two-thirds of the women were prescribed serum tumor marker assays. Possible explanations include the high frequency (~50%) of normal serum tumor marker status in stage I ovarian cancer (26), and the fact that several benign disorders (endometriosis, uterine fibroids, pelvic infection, etc.) can be accompanied by elevated serum tumor marker levels. Moreover, using a mathematical model, Timmerman et al underlined the low contribution of CA125 serum tumor marker to distinguish benign from malignant ovarian tumours (21). A previous study has also shown that the sensitivity and specificity of abnormal serum tumor marker status for malignant ovarian lesions are higher in menopausal women (27). In the present study, the main determinants of tumor marker assay prescription were older age, menopausal status, and ascitis on sonography.

Impact of preoperative determination of serum tumor markers on management of women with borderline ovarian tumor.

Interestingly, preoperative tumor marker assays modified patient management. Indeed, women who had these assays were more likely to have intra-operative histology and, hence, complete staging. Routine preoperative serum tumor marker assay raises issues of cost-effectiveness, and can generate anxiety if the results are abnormal. Several algorithms based

on epidemiological characteristics, serum tumor markers and sonography have been proposed for predicting the histological nature of adnexal masses (21). Despite their reported accuracy, routine use of such algorithms is limited by their complexity. In our study, multivariate analysis showed that abnormal preoperative serum tumor marker status influenced the surgical management of adnexal masses that were subsequently shown to be BOT. Although no report have focused on the prognostic relevance of abnormal serum tumor markers, our data underlined the risk of radical treatment in women with pre-operative abnormal tumor markers, even though there is no proven benefit for patients. Using preoperatively a multiple bioassay utilizing Human epididymal secretory protein E4 (He4) and CA125 in patients with a pelvic mass could be of interest in classifying patients in a high risk group of epithelial ovarian cancer (28). Serum He4 concentration may differentiate malignant ovarian tumors from endometriotic cysts (29-30). However, data concerning assessment of He4 especially in BOT are scarce and need further studies.

Impact of abnormal serum tumor markers on surgical management of women with borderline ovarian tumor

Abnormal serum tumor marker status was associated with first-line laparoscopy. There are several possible explanations for this apparent paradox. First, by permitting complete evaluation of the abdominal cavity, laparoscopy contributes to the choice of the surgical route. When macroscopic criteria suggest a benign tumor, an exclusively laparoscopic procedure is considered acceptable. In contrast, a median abdominal incision is often preferable when there are signs of malignancy. Second, laparoscopy permits adequate evaluation of the feasibility of optimal surgery or the need for neoadjuvant chemotherapy (31). Finally, laparoscopic surgery has been shown to be reliable for BOT (12-13, 22, 25, 32).

Relevance of serum tumor marker determination for recurrence detection.

The contribution of serum tumor markers to the follow-up of women with BOT is controversial. This could be due to the relatively low incidence of abnormal serum tumor markers in women with BOT, both preoperatively and during recurrences (8, 13, 22, 25, 32). In our study, only 83 (26.2%) of 317 women with BOT had routine serum tumor marker assays during follow-up, whereas our findings show that isolated abnormal serum tumor markers can lead to the diagnosis of recurrence.

There is no consensus on the indications of serum tumor marker assays in women treated for BOT. Despite both the low incidence of abnormal serum markers in women with BOT and their low contribution to differentiate benign from malignant ovarian tumors, our results support that the preoperative evaluation of serum tumors markers modified surgical management by increasing the use of first line laparoscopy, intra operative histology and complete staging. Previous studies have shown the high risk of recurrence of serous BOT, probably owing to the higher frequency of bilateral tumors than in women with mucinous BOT. Seidman and Kurman reported that women with serous BOT exhibiting micropapillary features, and women with mucinous BOT with intraepithelial carcinoma, had a higher risk of recurrence (33). Conservative surgery based on cystectomy exposes women to a high risk of persistent and/or recurrent BOT (7, 15, 32). As previously reported especially in case of invasive implants, women with FIGO stage > Ia BOT have a high risk of recurrence (32). Finally, nearly 80% of recurrences are diagnosed during the first two postoperative years (15, 22). It thus seems logical to recommend close follow-up of women treated for BOT, including serum tumor marker determination every 6 months for at least the first two postoperative years. This is particularly the case after conservative treatment, in patients with FIGO stage > Ia, and in patients with serous BOT with micropapillary features or mucinous BOT with intraepithelial carcinoma and in case of microinvasion on tumors or on implants. However, the use of CA125 in the follow up of patients with BOT has been recently discussed to detect

recurrence while representing a source of patient's anxiety (34). Further studies are required to evaluate the cost-effectiveness of CA125 determination in the follow-up of women with BOT.

Regarding the limitations of this study, its retrospective nature carries a risk of bias due to confounding factors. Also, our conclusions cannot be extended to patients with other complex but histological benign ovarian tumors. Tumor markers were not assayed in all the women who had recurrences, limiting the impact of our conclusions. Indeed, pre- and post-operative serum tumor markers determinations were not available for all patients experiencing a recurrence in stage I BOT. Moreover, no evaluation of CEA serum level according to smokers or non-smokers had been performed. However, this remains the largest study of the contribution of serum tumor markers to the management of borderline ovarian tumors.

In conclusion, our results suggest that serum tumor markers can improve the preoperative assessment and surgical management of BOT, notably by increasing the use of intra-operative histology. We therefore suggest evaluating serum tumor marker assays for all women with complex adnexal tumors. Moreover, isolated serum tumor marker abnormalities during follow-up can lead to the diagnosis of recurrence.

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Table 1: Preoperative CA125, CA19-9, CEA, and CA15-3 assay in women with serous and mucinous borderline ovarian tumors.

	CA125 N	CA19-9 N	CEA N	CA15-3 N	All tumor markers
Serous BOT					
Patients with tumor marker assays	113/181	45/180	59/180	13/181	13/181
Patients with at least one abnormal marker	51/113	8/45	2/59	2/13	
Mucinous BOT					
Patients with tumor marker assays	89/136	46/132	52/133	10/133	10/136
Patients with at least one abnormal marker	31/89	11/46	4/52	2/10	

Table 2: Epidemiologic characteristics of women with serous or mucinous borderline ovarian tumours according to tumour marker status.

Criteria	Patients with marker assays (n=205)	Patients without marker assays (n=112)	P
Age (mean±SD)	49.0 ± 1.1	42.8 ± 1.5	0.001
Parity (mean±SD)	1.5 ± 0.1	1.2 ± 0.1	0.03
Nulliparous	64/205	52/112	0.01
Post-menopausal	84/202	30/110	0.017
Ascitis on sonography	25/86	5/45	0.09
Preoperative abdominopelvic CT	67/161	17/86	<0.0001
Preoperative abdominopelvic MRI	22/157	5/96	0.03
Peritoneal washing	155/204	48/111	<0.0001
Omentectomy	88/205	35/111	0.06
Random peritoneal biopsies	92/205	20/110	<0.0001
Intra-operative histology	108/159	24/67	<0.0001
Conservative treatment	77/205	68/112	0.0001
Complete staging during first surgery	49/178	10/90	0.004
Recurrence	13/205	16/112	0.03

Patients with missing data were excluded from the analysis.

Table 3: Impact of abnormal serum tumor markers on surgical management of women with serous or mucinous borderline ovarian tumors who had tumoral marker assays.

Characteristic	Abnormal marker status (93 patients)	Normal marker status (112 patients)	P
Exclusive laparoscopic surgery	16/29	40/50	0.007
Converted laparoscopy	13/29	10/50	0.007
First-line laparotomic surgery	64/93	62/112	0.007
Intra-operative histology	53/68	49/80	0.04
Complete staging during first surgery	33/79	15/88	0.0008

Patients with missing data were excluded from the analysis.

Table 4: Logistic regression analysis with first-line laparoscopy as the response variable and including serum marker levels as the explanatory variable (number of observations = 69).

Parameters selected	Univariate analysis			Multivariate analysis		
	OR	95%CI	<i>p</i> -value	Adjusted OR	95%CI	<i>p</i> -value
Clinical						
Age (years)	0.97	0.96-0.99	0.0001			
HRT	1.53	0.66-3.54	0.32			
Nulliparity	1.75	1.11-2.79	0.02			
Infertility	3.27	1.55-6.91	0.007			
Family history	0.98	0.51-1.90	0.95			
Imaging						
US visible ascitis	0.22	0.09-0.59	0.001	0.03	0.00 – 0.55	0.02
US tumor size (mm)	0.84	0.79-0.89	$<10^{-4}$	0.78	0.66 – 0.92	0.003
US bilateral tumor	0.91	0.50-1.65	0.76	0.05	0.01 – 0.55	0.01
Biological						
Abnormal serum markers	0.56	0.31-1.02	0.06	9.63	1.40 – 66.39	0.02

OR= odds ratio; 95% CI = 95% confidence interval; Blank cells indicate that the variable was not included in the final model.

The model χ^2 was 46.5, df: 6, $p=10^{-4}$.

Table 5. Logistic regression analysis with post-operative recurrence as the response variable (number of observations =170).

Parameters selected	Univariate analysis			Multivariate analysis		
	OR	95%CI	<i>p</i> -value	Adjusted OR	95%CI	<i>p</i> -value
Clinical						
Age (years)	0.94	0.91-0.96	0.0001			
Nulliparity	4.02	1.81-8.92	0.003			
Infertility	3.68	1.47-9.17	0.0003			
Family history	1.38	0.50-3.86	0.53			
Imaging						
US visible ascitis	2.09	0.60-7.29	0.24			
US tumor size (cm)	0.98	0.91-1.05	0.60			
US bilateral tumor	2.20	0.95-5.10	0.06			
Biological						
Serum markers level	3.30	0.85-12.85	0.07	1.97	0.44-8.83	0.79
Surgical						
Conservative treatment	4.39	1.83-10.55	0.0004	4.44	1.10-18.00	0.04
FIGO stage Ia vs others	3.19	1.46-6.97	0.0002	7.84	1.73-35.48	0.0008

OR= odds ratio; 95%CI = 95% confidence interval; * This variable was forced into the model; Blank cells indicate that the variable was not included in the final model. The model χ^2 was 14.0, df: 3, $p=0.003$.