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Risk factors for recurrence of borderline ovarian tumors in France: A multicenter retrospective study by the FRANCOGYN group

E. Sangnier[1], L. Ouldamer[2,3], S. Bendifallah[4], C. Huchon[5], P. Collinet[6], A. Bricou[7], C. Mimoun[8], L. Lecointre[9], O. Graesslin[1], E. Raimond[1]

For the Research group FRANCOGYN.

Authors' affiliations:

[1]Department of Obstetrics and Gynaecology, Institute Alix de Champagne University Hospital, Reims Champagne Ardennes university, Reims, France
[2]Department of Obstetrics and Gynaecology, Regional University Hospital Center of Tours, Bretonneau Hospital, Tours, France
[3]INSERM U1069; Université François-Rabelais, Tours, France
[4]Department of Obstetrics and Gynaecology, Tenon Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris, France
[5]Department of Obstetrics and Gynaecology, Intercommunal Hospital Center of Poissy, Poissy, France
[6]Department of Obstetrics and Gynaecology, Regional University Hospital Center of Lille, Lille, France
[7]Department of Obstetrics and Gynaecology, Jean Verdier Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris, France
[8]Department of Obstetrics and Gynaecology, Lariboisière University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), University Paris 7, Paris, France
[9]Department of Obstetrics and Gynaecology, University Hospital Center, Strasbourg, France

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Short running title: Risk factors for BOT recurrence

Corresponding author*:

Emilie RAIMOND MD, Department of Obstetrics and Gynecology, Maison Blanche Hospital, 45 rue Cognacq Jay, 51092 Reims Cedex, France.
Phone: 33-326-787-648, Fax: 33-326-783-839

e-mail: eraimond@chu-reims.fr

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ABSTRACT

Introduction: Borderline ovarian tumors (BOTs) although rare, have shown an increase in the incidence worldwide. Although the survival rate is high, the recurrence rate is estimated to be between 5% and 34%. The objective of this study was to identify risk factors for recurrence of BOTs.

Methods: This retrospective multicenter study included 493 patients treated surgically for BOT between January 2001 and December 2018.

Results: Thirty-seven patients showed recurrence (group R, 7.5%), while 456 did not (group NR, 92.5%). With an average follow-up of 30.5 months (1-276), the overall recurrence rate was 7.5%. Recurrence rates for the BOT and invasive types were 5.7% (n=28) and 1.4% (n=7), respectively. The mean time to recurrence was 44.1 (3-251) months. Univariate analysis showed that age at diagnosis, type of surgical procedure, histological type, and FIGO stage were factors influencing recurrence. Multivariate analysis showed that the risk factors for recurrence of BOT were conservative treatment (OR=7 [95% CI 3.01-16.23]; $p<0.05$) and advanced FIGO stage (OR=5.86 [95% CI 2.21-15.5]; $p<0.05$).

Discussion: To the best of our knowledge, this multicenter study was one of the largest studies on the risk factors for BOT recurrence. Conservative treatment and advanced FIGO stage were identified as risk factors for BOT recurrence. These results reinforce the need for restaging of patients who did not have an optimal initial surgical staging so as not to avoid missing a tumor in the advanced stage. Referral to a surgical oncology center is suggested to optimize overall patient management.

Key words : Borderline, ovarian tumor, recurrence, risk factors

GLOSSARY

BOT : Borderline Ovarian Tumor

FIGO : International Federation of Gynaecology and Obstetrics

HRT : hormone replacement therapy

WHO : World Health Organization

INTRODUCTION

Borderline ovarian tumors (BOTs) account for 10%-20% of epithelial tumors of the ovary (1-3). They are rare tumors, but their incidence is increasing, estimated at 1.8 to 4.8 per 100,000 women per year worldwide (4,5).

BOT is defined as a tumor with a borderline quota of strictly more than 10% (1). They differ clinically from ovarian cancers by showing good prognosis and the patients are 10 years younger at the time of diagnosis, with a higher proportion of patients in the reproductive age group (2,7). Although the survival rate is estimated to be 100% and 92% at 5 and 10 years, respectively, the recurrence rate is estimated to be between 5% and 34% depending on the studies (7-9). Most often, the recurrence is in the form of BOT but there are recurrence in the invasive cancer form (7-9).

Conservative surgery is recommended in young women who wish to preserve their fertility, regardless of the stage of the tumor (9-13). The challenge in the surgical management of BOT is to facilitate conservative treatment while allowing complete staging in order to limit the risk of recurrence in the invasive form (11). A number of studies have attempted to identify the risk factors for recurrence of BOTs; however, these were mainly small studies with short follow-up periods and not consensual histopathological definition of borderline ovarian tumors, which have led to classification bias and inconsistent results depending on the study.

The objective of our study was to identify risk factors for recurrence of BOTs.

MATERIALS AND METHODS

Population

This retrospective multicenter study was conducted from January 2001 to December 2018 by obtaining data from 7 French cancer centers belonging to the FRANCOGYN research group. Patient epidemiological data, medical and surgical history, tumor markers, surgical procedures performed, histological characteristics of tumors, and International Federation of Gynaecology and Obstetrics (FIGO) stages were collected from each center and anonymized.

French-speaking women aged ≥15 years (parental consent was obtained for minors) affiliated with the social security system who had undergone surgery for treatment of serous or mucinous BOT between January 2001 and December 2018 were included in the study.

Patients with borderline quotas of <10% after centralized re-reading of the slides, missing data concerning recurrence status, and rare histological types (clear cell tumors, Brenner's tumors, and endometrioid tumors) were excluded from the study.

In accordance with the French law, this retrospective study of medical records was authorized by MR-004. Participants were informed that their information might be used for biomedical research purposes and that they had the right to object.

Definitions and procedures

Patients were divided into 2 groups according to whether they had a recurrence (group R, 7.5%) or not (group NR, 92.5%). Recurrence was suspected based on clinical, biological, or radiological data and after histological confirmation. The recurrence could be of BOT type or infiltrating cancer type.

The tumor stage was defined according to the FIGO 2014 classification of ovarian tumors (14). Peritoneal implants were classified as invasive and non-invasive (15). Microinvasive tumors were defined as those with <5 mm invasion of the stroma (6).

Conservative treatment was defined as a surgical procedure preserving the uterus and at least part of an ovary to allow subsequent fertility (16). The recommended peritoneal staging included peritoneal cytology, extensive omentum biopsy or omentectomy, multiple peritoneal biopsies, and appendectomy in the case of mucinous type tumor (11-13). This was performed during the initial surgery (Surgery 1) when the diagnosis of BOT was confirmed by extemporaneous examination. Otherwise, or in case of incomplete staging, it was performed during a second surgery (Surgery 2).

The recurrence period in months was defined as the time elapsed between the date of the first surgery and the date of discovery of the recurrence.

Statistical analyses

A univariate analysis was used to assess :

- patient characteristics : age, hormonal status, smoking, use of hormone replacement therapy (HRT), past medical history.
- tumor characteristics : bilateral involvement, micropapillary contingent, FIGO stage, peritoneal implants, peritoneal cytology.
- the surgical procedure performed : surgery approach, conservative or non-conservative treatment.

Categorical variables were compared using the chi-squared test or the Fisher exact test when the validity conditions for chi-squared test were not met. To compare a continuous variable with a categorical variable, we used the Student's *t*-test or the Wilcoxon's test when the variable did not follow a normal distribution.

Multivariate analysis was performed using a logistic regression model including factors that were significant in the univariate analysis.

For the survival data, the curves were produced by the Kaplan-Meier method. The survival analysis was performed with a Cox model. Odds ratio was calculated with a 95% confidence interval. The test results were considered significant when the p-value was <0.05.

The data were managed in an Excel database (Microsoft, Redmond, WA). The statistical analyses were performed using the software R 2.15.3 package and library Verification, HMISC, survival, RMS, and stats available online (http://lib.stat.cmu.edu/R/CRAN/).

RESULTS

From January 2001 to December 2018, 564 patients were treated for BOT. After centralized re-reading of the slides, 71 patients were excluded from the analysis, of whom 43 had missing recurrence status data, 22 had rare histological types, 2 had BOTs with a borderline quota <10%, and 4 had invasive carcinomas. A total of 493 patients were included from 7 French cancer centers: Lariboisière hospital in Paris (n=59), the intermunicipal hospital center in Poissy (n=36), Jean Verdier hospital in Bondy (n=27), and the University Hospital Centers in Tours (n=142), Lille (n=104), Strasbourg (n=93), and Reims (n=32). Of these patients, 37 showed recurrence (group R, 7.5%) and 456 did not (group NR, 92.5%).

The mean age at diagnosis was 48.8 years (15-92 years). In 33.3% of cases, patients were less than 40 years old (n=164) and 29.6% were nulliparous (n=146). A laparoscopy was performed first in 59.2% of cases (n=292). In 28% of cases, the final treatment was conservative (n=138) and complete final staging was performed as recommended in 74% of cases (n=365). The mean tumor size was 11.7 cm (1-35 cm), and the intraoperative tumor rupture rate was 13.8% (n=68). Histologically, 51.9% of cases showed serous tumors, while the remaining 48.1% of cases were mucinous. Peritoneal implants were found in 13.4% of patients (n=66) and in 2%

were invasive (n=10). As for the FIGO stage, a majority of patients had FIGO I (83.4%, n=411). The clinical characteristics of the patients included in the study have been summarized in **Table 1**.

The average follow-up of patients was 30.5 months (1-276 months). The overall recurrence rate was 7.5% (n=37). Recurrence was BOT and invasive types in 5.7% (n=28) and 1.4% (n=7) of cases, respectively. The mean overall recidivism time was 44.1 months (3-251 months), the mean BOT recidivism time was 47.6 months (3-251 month), and the mean invasive relapse time was 26.6 months (8-54 months). The mean age of patients at the time of recurrence was 35.1 years (18-70 years). Patients with recurrence were significantly younger than those without (35.1 versus 51 years; OR=0.94 [95% CI 0.92-0.96]; p<0.05) (**Table 2**).

Univariate analysis for comparison of patients in the R and NR groups found that conservative treatment was associated with risk of recurrence compared to radical treatment (OR=0.14 [95% CI 0.004-0.450]; p<0.05). Similarly, advanced FIGO stage and serous type of tumor were associated with risk of recurrence compared, respectively, to early FIGO stage (OR=6.88 [95% CI 3.6-14.5]; p<0.05) and to mucinous type of tumour (OR=2.03 [95% CI 1.0-4.1]; p=0.05).

Conservative treatment was performed in 67.6% compared to 24.8% in the R group (OR=6.29 [95% CI 2.9-14.2]; p<0.05). The implant rate was higher in the R group (43.2%) than that in the NR group (OR=6.15 [95% CI 2.8-13.3]; p<0.05). Lastly, there were 40.5% of advanced FIGO stage in the R group compare to 10% in the NR group (OR=6.19 [95% CI 2.78-13.5]; p<0.05) **(Table 2).**

In multivariate analysis, the type of surgical treatment, particularly conservative treatment (OR=7 [95% CI 3.01-16.23]; p<0.05), and the advanced FIGO stage of the tumor (OR=5.86 [95% CI 2.21-15.5]; p<0.05) appeared to significantly influence the risk of recurrence (**Table 3**). Similarly, the survival curves showed a reduction in the recurrence-free survival with conservative treatment and with advanced FIGO stage (II/III) (p<0.05) (**Figures 1 and 2**).

DISCUSSION

This study identified two risk factors for BOT's recurrence: conservative treatment (OR=7 [95% CI 3.01-16.3]; p<0.05) and advanced FIGO stage of the tumor (OR=5.86 [95% CI 2.21-15.5]; p<0.05).

BOTs mainly affect young patients of childbearing age, hence it is challenging to provide conservative treatment to patients who so wish, without increasing the risk of recurrence, despite excellent prognosis (7-9).

In this study, conservative treatment was observed as a risk factor for recurrence (OR=7 [95% CI 3.01-16.2]; p<0.05), which is in accordance with reports in the literature (9,10,16-19). Helpman *et al.* showed that conservative surgery was independently associated with recurrence (HR=2.57 [95% CI 1.1-6.0]; p=0.029) without impact on overall survival, while Vasconcelos *et al.* showed that among conservative treatments, unilateral cystectomy was associated with increased rate of recurrence than unilateral adnexectomy (p<0.0001) (17,19). These results were confirmed by two studies that proposed a predictive model of recurrence risk in which cystectomy was associated with an increased risk of recurrence at 5 years (OR=11.35 [95% CI 4.01-32.1]; p<0.001) (9,20). Despite this, cystectomy is preferred in young women wishing to preserve their fertility, regardless of the FIGO stage of the tumor. Indeed, a study by Palomba *et al* precised that for ultra conservative fertility surgery, time to first recurrence was significantly shorter but without any difference in the recurrence free survival between bilateral cystectomy group and unilateral adnexectomy with contralateral cystectomy group (p=0,41). Moreover, this study showed a higher pregnancy rate (OR=8.05 [95% CI 1.20-9.66]; p<0.01) with a shorter delay (p<0.02) in bilateral cystectomy (21). In addition, increase in the recurrence rate after conservative surgery had no impact on the overall survival (p=0.91), which explains the preference for cystectomy in young women with a desire for pregnancy and adnexectomy in postmenopausal women (11-13,22).

Advanced FIGO stage (II/III) was a risk factor for recurrence of BOT in this study (OR=5.86 [95% CI 2.21-15.5]; p<0.05). This result was consistent with that reported in the literature, particularly in the studies by Ewald-Riegler *et al.* (HR=37.1 [95% CI 4.5-155.5]), Delle Marchette *et al*. (HR=3.18 [95% CI 2.11-4.78]; p<0.001) and Vo *et al.* (HR=4.44 [95% CI 1.60-12.38]) in which advanced FIGO stage increased the risk of BOTs recurrence (23-25). Therefore, extraovarian extent of the disease appears to increase the risk of recurrence, even in the case of complete carcinologic surgery.

Patients with recurrence were significantly younger than those without (35.1 versus 51 years; OR=0.94 [95% CI 0.92-0.96]; p<0.05). However, multivariate analysis did not show a relationship between patient age and risk of recurrence. In the literature, age was found to be a prognostic factor for recurrence of BOTs (16,20,26). Indeed, owing to longer life expectancy, young patients are theoretically at greater risk of recurrence, as recurrence of BOTs may occur after a long period, sometimes more than 15 years after initial management (7). This study had a shorter follow-up period (30.5 months) compared with that reported in the literature; this may explain why this factor was not found to be associated with recurrence in the multivariate analysis. In fact, 24.3% of our patients had a follow-up of 12 months or less (n=120), explained by the post-operative monitoring often carried out by the patient's usual gynecologist outside the expert center that carried out the study (**Table 4**).

In this study, 74% of the staging was performed as recommended (n=365) and no link with recurrence was found. Similarly, the study by Fauvet *et al.* found no link between recurrence and restaging surgery (27). Conversely, several studies observed an increase in the recurrence rate proportional to the number of missing procedures, with omentectomy being the procedure with the greatest impact (HR=1.91 [95% CI 1.15-3.19]; p=0.013) (26,28,29). These studies also found a low rate of procedures, between 31.7% and 49.7%, in compliance with the recommendations, which was a bias in the analysis of recurrences with a risk of under-evaluating the FIGO stages and performing incomplete resection with tumor residue. The main interest of a complete staging would be to avoid missing the presence of implants in order not to under-

diagnose patients. The high rate of complete staging reported in this study (74%) was a strength, and was probably an explanation of the low recurrence rate (7.5%) (**Table 4**).

CONCLUSION

To the best of our knowledge, this multicenter study is the largest French study on the risk factors for BOTs and one of the largest internationally. Conservative treatment and advanced FIGO stage of the tumor were found as risk factors.

These results confirms the need for restaging surgery for patients who have not had optimal initial surgical staging by to avoid to ignore an advanced tumor stage. Referring patients to an oncology center may allow us to optimize their management.

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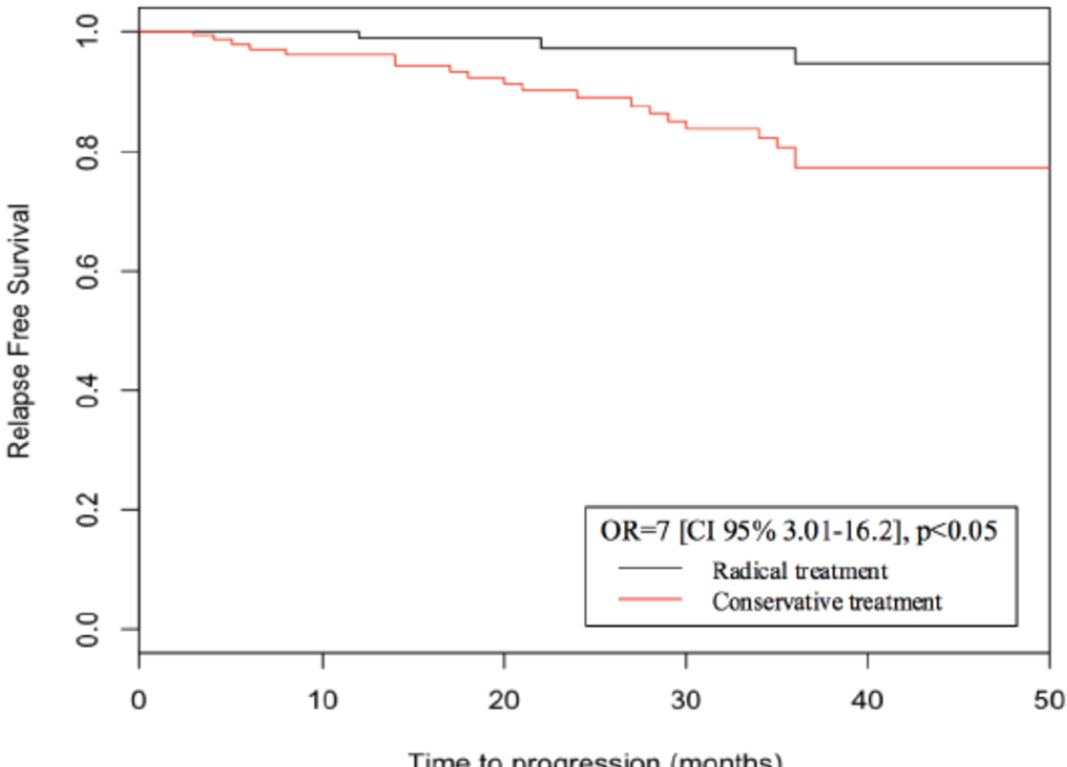
Relapse Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Time to progression (months)
OR=7 [CI 95% 3.01-16.2], p<0.05
Radical treatment
Conservative treatment

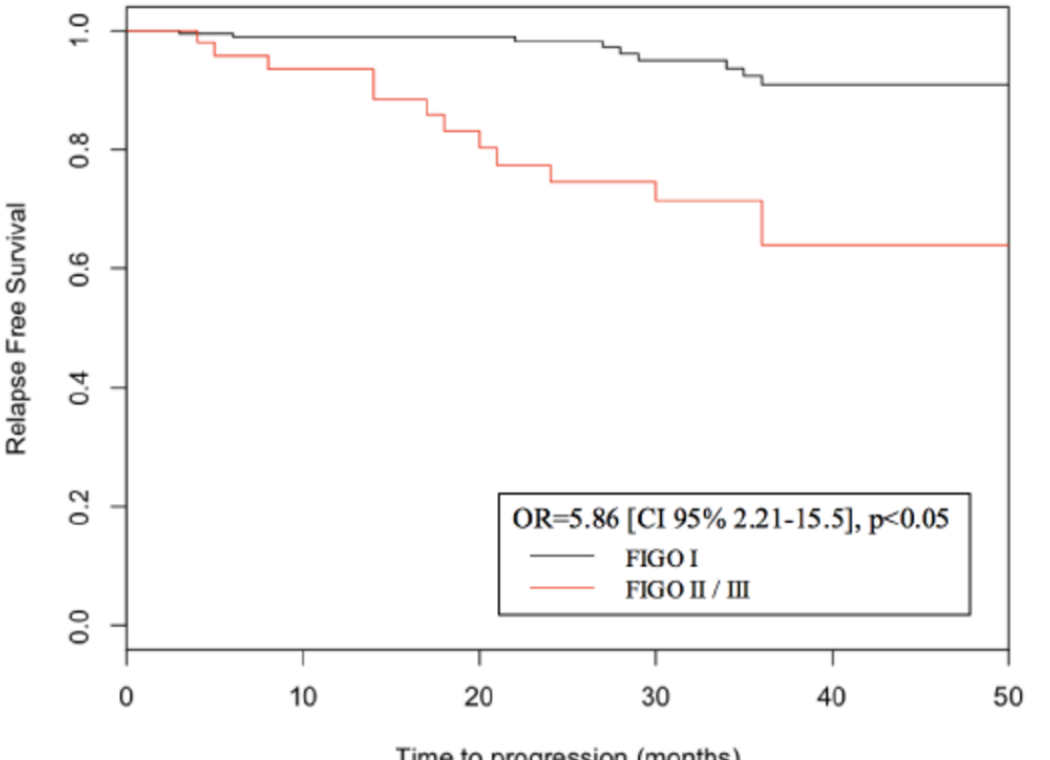
Relapse Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Time to progression (months)
OR=5.86 [CI 95% 2.21-15.5], p<0.05
FIGO I
FIGO II / III

Table 1 : Clinical and paraclinical characteristics of the population

Characteristics	n = 493
Population	
Mean age (years)	48.8 (15-92)
Age under 40 y	164 (33.3%)
Mean BMI (kg/m2)	26.2 (15.6-66.6)
Nulliparity	146 (29.6%)
Menopause	148 (30%)
Taking of HRT	8 (1.6%)
Active smoking	70 (14.2%)
Medical past history	
Ovarian stimulation	16 (3.2%)
Endometriosis	10 (2%)
Family ovarian cancer	7 (1.4%)
Surgical procedures	
Initial laparoscopy	292 (59.2%)
Conservative treatment	
Initial (surgery 1)	202 (41%)
Final (surgery 1 and 2)	138 (28%)
Recommended staging	
Initial (surgery 1)	229 (46.5%)
Final (surgery 1 and 2)	365 (74%)
Histopathology	
Histological type	
Serous tumor	256 (51.9%)
Mucinous tumor	237 (48.1%)
Bilateral	74 (15%)
Positive peritoneal cytology	69 (14%)
Micropapillary content	42 (8.5%)
Implants	
Non invasive	66 (13.4%)
Invasive	10 (2%)
Definitive FIGO stage	
Early stage (I)	411 (83.4%)
Advanced stage (≥ II)	60 (12.2%)

Data : average (minimum-maximum) et number (%), BMI : Body Masse Index, HRT : Hormone Replacement Therapy
FIGO : International Federation of Gynaecology and Obstetrics, Surgery 1 : Initial procedure, Surgery 2 : Restaging procedure

Table 2 : Population characteristics about recurrence status in univariate analysis

Characteristics	Group R (n = 37)	Group NR (n = 456)	OR [CI 95%]	*P* value
Population				
Mean age (years)	35.1 (18-70)	51 (15-92)		**<0.05**
Age under 40 yo	28 (75.7%)	62 (13.6%)		0.06
Mean BMI (kg/m2)	25.5 (18.4-45.2)	26.4 (15.6-66.6)		**<0.05**
Nulliparity	22 (59.5%)	60 (13.2%)	9.6 [4.5-21.1]	**<0.05**
Menopause	5 (13.5%)	79 (17.3%)		0.66
Taking of SHT	0	5 (1.1%)		0.88
Active smoking	4 (10.8%)	25 (5.5%)		0.71
Medical past history				
Ovarian stimulation	2 (5.4%)	11 (2.4%)		0.93
Endometriosis	1 (2.7%)	5 (1.1%)		1
Family ovarian cancer	0	3 (0.7%)		0.82
Surgical procedures				
Surgical approach (1)				
Laparotomy	12 (32.4%)	188 (41.2%)		0.3
Laparoconversion	4 (10.8%)	56 (12.3%)		0.62
Surgical treatment (2)				
Unilateral adnexectomy and controlateral cystectomy	5 (13.5%)	9 (2%)		0.08
Unilateral adnexectomy	16 (43.2%)	126 (27.6%)		0.67
Blateral adnexectomy	6 (16.2%)	270 (59.2%)		**<0.05**
Bilateral cystectomy	3 (8.1%)	5 (1.1%)		0.11
Conservative treatment				
Initial (surgery 1)	30 (81.1%)	172 (37.7%)	7.07 [2.95-19.4]	**<0.05**
Final (chirurgie 1 et 2)	25 (67.6%)	113 (24.8%)	6.29 [2.9-14.2]	**<0.05**
Recommended staging				
Initiale (chirurgie 1)	9 (24.3%)	220 (48.2%)	0.35 [0.14-0.77]	**<0.05**
Final (surgery 1 and 2)	24 (64.9%)	341 (74.8%)		0.2
Anatomopathology				
Histological type				
Serous tumor	25 (67.6%)	231 (50.7%)		0.06
Mucinous tumor	12 (32.4%)	225 (49.3%)		0.06
Bilateral	13 (35.1%)	61 (13.4%)	3.5 [1.5-7.6]	**<0.05**
Positive peritoneal cytology	14 (37.8%)	55 (12.1%)	4.42 [1.98-9.59]	**<0.05**
Micropapillary content	4 (10.8%)	38 (8.3%)		0.83
Implants				
Total (3)	16 (43.2%)	50 (11%)	6.15 [2.8-13.3]	**<0.05**
Non invasive	13 (35.1%)	43 (9.4%)		**<0.05**
Invasive	3 (8.1%)	7 (1.5%)		**<0.05**
Definitive FIGO stage				
All	-	-		
Early stage (I)	19 (51.4%)	392 (86%)	0.17 [0.08-0.37]	**<0.05**
Advanced stage (≥ II)	15 (40.5%)	45 (10%)	6.19 [2.78-13.5]	**<0.05**

Data : average (minimum-maximum) et number (%)

(1) Reference parameter : laparoscopy, (2) Reference parameter : Unilateral cystectomy , (3) Reference parameter : No implant

BMI : Body Masse Index, HST : Hormonal Substitutive treatment

FIGO : Fédération Internationale de Gynécologie Obstétrique

Surgery 1 : Initiale, Surgery 2 : Restaging procedure

Table 3 : Recurrence risk factors in multivariate analysis

Characteristics	OR [CI 95%]	*P* value
Age at diagnosis	0.98 [0.94-1.02]	0.29
Type of treatment	0.20 [0.036-1.62]	**<0.05**
Histological type	1.15 [0.45-2.93]	0.77
FIGO stage	5.86 [2.21-15.5]	**<0.05**

Data : average (minimum-maximum) et number (%), FIGO : International Federation of Gynaecology and Obstetrics
CI: Confidence Intervalle

Table 4 : Literature review on recurrence rate and follow-up timep

Studies	Years	Patients (n)	Follow up (month)	Recurrence (%)
Fauvet et al. [27]	2004	360	37 +/- 44	9.4
Fauvet et al. [18]	2005	358	36.6 +/- 41	10.3
Romagnolo et al. [30)]	2005	113	44 (6-122)	11.5
Fauvet et al. [10]	2005	360	NC	10
Park et al. [22]	2009	360	70 (3-216)	5
Zapardiel et al. [31]	2010	70	60.5	14.3
Ewald-Riegler et al. [23]	2012	158	42.1	11.4
Azuar et al. [26]	2013	142	80.5	7.7
Bendifallah et al. [9]	2014	186	94.9 (60-207)	34.4
Bendifallah et al. [32]	2016	428	94.9	23.8
Helpman et al. [19]	2017	213	75	23.5
Ouldamer et al. [20]	2017	360	60 (1-320)	20
Delle Marchette et al. [24]	2019	535	148.8 +/- 7,2	35.9
Vo et al. [25]	2019	433	43 (3-105)	4.2
Our study	**2020**	**493**	**30.5 (1-276)**	**7.5**