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Fertility-sparing treatment in advanced-stage serous borderline ovarian tumors. An analysis from the MITO14 study database

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HIGHLIGHTS

- Despite the high rate of recurrence, FSS provides good reproductive outcomes without a negative impact on overall survival.
- The presence of invasive peritoneal implants affects the disease-free outcome with no impact on overall survival.
- Advanced-stage serous BOTs can be safely selected for fertility-preservation management.

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ABSTRACT

Objectives. To evaluate oncological and reproductive outcomes of women undergoing fertility-sparing surgery (FSS) for stage II–III serous borderline ovarian tumors (BOTs).

Methods. A multi-institutional retrospective study was conducted within the MITO Group.

Results. A total of 91 patients were recruited. The median follow-up time from primary cytoreduction was 127 months (IQR range 91–179). Forty-nine patients (53.8%) experienced at least one recurrence (median time to first relapse 22 months, IQR range 9.5–57). At univariable analysis, significant predictors of relapse were: size of largest extra-ovarian lesion, peritoneal cancer index, completeness of cytoreduction, type of implants. After multivariable analysis, the size of extra-ovarian lesions and the presence of invasive implants resulted as the only independent predictors of recurrence. Median disease-free survival (DFS) was 96 months (95% CI, 24.6–167.3), while median disease-specific survival (DSS) was not reached. Twenty-nine patients (31.8%) attempted to conceive: 20 (68.9%) achieved at least one pregnancy and 18 (62%) gave birth to a healthy child. At the end of the observation period, 88 patients (96.7%) showed no evidence of disease, 2 (2.2%) were alive with disease, and 1 patient (1.1%) died from BOT.

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Conclusions. Despite the recurrence high rate, FSS provides good chances of reproductive success with no impact on DSS. The presence of invasive peritoneal implants affects the DFS but not DSS nor reproductive outcome. The risk of recurrence would not seem to be related to the ovarian preservation per se, but to the natural history of the initial peritoneal spread.

1. Introduction

Borderline ovarian tumors (BOTs) are rare neoplasms, representing 10% to 20% of all ovarian epithelial tumors [1]. Approximately 50–55% of BOTs are serous and one third of serous BOTs are associated with peritoneal implants [2–4]. In contrast to patients with frankly invasive ovarian carcinoma, women with BOT tend to be younger and to have a better overall survival [5,6]. To date, fertility-sparing surgery (FSS) is the standard management of young patients with BOT limited to one or both ovaries [5–7]. For serous BOTs with peritoneal implants, data concerning the efficacy and safety of FSS are very limited and mostly based on small retrospective series generally in the absence of long-term treatment outcomes [8–13]. Thus, it has not yet been possible to draw definitive conclusions on the conservative approach in this setting of patients.

It is definitely acknowledged that FSS for early stage BOTs is associated with an increased risk of recurrence with no significant impact on survival [6,7,14,15]. Moreover, in serous BOTs there is some evidence that: i) FSS in advanced-stage is associated with a higher risk of recurrence than in early-stage disease; ii) rarely recurrences present with malignant transformation [7,14,15]. Therefore, in a context of advanced-stage serous BOTs, the decision making process with respect to a fertility-sparing management must take into consideration both the risk of relapse and the risk of malignant recurrence/progression to invasive carcinoma.

In 2011, the Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO) group endorsed a retrospective/prospective project among its surgical membership aimed at registering BOTs in a centralized database. The main purpose of this multicentre project was to collect a large series of cases allowing to draw a reliable picture of the management of BOTs within the group and evaluate long-term outcomes. The current study presents the results of an unplanned analysis, aimed to show the oncological and reproductive outcomes of women recorded into the aforementioned database and undergoing FSS for stage II – III serous BOTs.

2. Materials and methods

The *MITO14* is a multi-institutional retrospective/prospective study conducted among MITO affiliate centres with the aim of systematically collecting data from consecutive BOT patients in a centralized database. Data are recorded using dedicated electronic Case Report Forms.

In the present article, data are presented on women with advanced-stage serous BOT registered into the *MITO14* database and conservatively treated between January 1995 and December 2019. All retrieved cases were from Cancer Centres or University Hospitals where pathologic revision was performed by institutionally dedicated pathologists according to $WHO_{2014,2020}$ (classification of BOTs) and Bell's criteria (extra-ovarian implants) as indicated by the ESGO last consensus conference [2,3,6,16].

The primary objectives for this analysis were: i) to evaluate the recurrence rate and to determine predictors of recurrence; ii) to assess the impact of a fertility-sparing treatment on disease-free survival (DFS) and disease-specific survival (DSS). The secondary objective was to evaluate pregnancy and live birth rates following treatment.

The Institutional Review Boards (IRB) of participating centres approved the study, except for those where analyses of existing data were exempt from formal IRB approval. All patients included in the present analysis gave written consent to data collection and to the use of personal records for health research, in the absence of any identifiers linking individuals to the data.

Only patients undergoing fertility-sparing surgery and with histologically proven $FIGO_{2014}$ stage II – III serous BOTs at final pathology were included in the present analysis. Cases submitted to bilateral salpingo-oophorectomy with uterine preservation were also included.

The following exclusion criteria were considered: i) age > 45 years; ii) non-serous histological subtypes; iii) presence of second tumor (s) treated by laparotomy or requiring therapy interfering with the treatment of BOT.

All data were checked for plausibility and completeness by two authors (FF, SG). In particular, data were collected on: patient- (age; body mass index; pregnancies); disease- (preoperative CA125 serum level; FIGO stage; tumor dissemination pattern), and treatment-related characteristics (surgical approach and procedures; completeness of cytoreduction; intra−/post-operative complications; adjuvant therapies). Primary and restaging surgical procedures eventually performed were considered together. All surgical reports were aligned with pathology reports.

The extent of peritoneal dissemination at the time of surgery was scored according to the Peritoneal Cancer Index (PCI) [17]. Completeness of surgical cytoreduction was categorized as proposed by Sugarbaker [17]: no visible residual tumor (CC =0), residual nodules ≤0.25 cm (CC =1), between 0.26 and 2.5 cm (CC =2), and > 2.5 cm (CC =3). Post-operative complications were considered within 30 days from hospital discharge, and graded according to the Clavien-Dindo classification [18]. Disease recurrences were registered together with details about their occurrence time, localization and treatment. Patient follow-up data were gathered until the end of June 2020.

2.1. Statistical analysis

Categorical and continuous variables were reported as frequency and percentage and as median and interquartile range (IQR), respectively.

The univariable associations of demographic and clinico-pathologic characteristics with the occurrence of disease recurrence were evaluated using the Fischer's exact test, the $\chi 2$ test, and the nonparametric Mann-Whitney test, as appropriate.

The relative importance of variables as independent predictors of recurrence was analysed with the multivariable Cox proportional hazard regression: to correct for possible confounders, all parameters found to have a $p < 0.05$ at univariable analysis were included into the multivariable Cox regression model; adjusted hazard ratios (HR) and 95% CI for prognostic factors were estimated.

DFS was calculated by the date of surgery until the date of first disease recurrence or death, whichever occurred first. Patients who did not experience recurrence were censored on the date of the last follow-up visit. DSS was defined as the time that elapsed from the date of surgery to the date of death, or of the last follow-up visit for living patients. Survival curves were generated with Kaplan-Meier method.

All *p-values* were two sided, and statistical significance was set at $p < 0.05$. Statistical analysis was performed with SPSS statistical software version 21.0.

3. Results

A total of 91 patients with FIGO$_{2014}$ stage II – III serous BOTs, undergoing fertility-sparing treatment in 14 Centres, were recruited from the overall *MITO14* database ($N = 1390$), and included in the present analysis (Fig. 1). The median follow-up time from primary cytoreduction was 127 months (IQR range 91–179 months). Patient, tumor- and treatment-related characteristics at the time of conservative surgery are detailed in Table 1.

Most patients presented with serous BOTs at stage III (56%). Extra-ovarian invasive implants were found in 14.3% of cases. The majority of patients suspected for bilateral ovarian involvement were treated with unilateral salpingo-oophorectomy and contralateral cystectomy (30/41; 73.1%), 6 (14.6%) with bilateral cystectomy, and the remaining 5 (12.2%) with bilateral salpingo-oophorectomy (and uterine preservation) due to bulky (≥7 cm) involvement of both ovaries. Bilateral ovarian involvement, however, resulted at final pathology in (36/91) 39.6%.

Complete (CC =0) cytoreduction was achieved in 83 patients (91.2%), with a further 3 patients (3.3%) showing ≤0.25 cm residual tumor (CC =1), and the remaining 5 (5.5%) >0.25–2.5 cm residual nodules (CC =2). Surgical procedures are detailed in Table 2.

Post-operative severe (grade 3, 4) complications occurred in 2.2% (2/91), with no cases of peri-operative mortality. In particular, a reoperation was required in 2 patients for post-operative bleeding (1) and surgical wound dehiscence (1). A total of 14 (15.3%) patients (6 with invasive implants) received chemotherapy after primary cytoreduction (platinum combination in 7, single agent platinum in the remaining 7).

Forty-nine patients (53.8%) experienced at least one recurrence: 11 of the 13 (84.6%) patients with extra-ovarian invasive implants, and 38 of the 78 (48.7%) with non-invasive implants ($p = 0.016$). The median time from the primary cytoreduction to first relapse was 22 months (IQR range 9.5–57 months), not significantly different between patients with non-invasive and invasive implants (median time to recurrence: 22.5 months vs 17 months, $p = 0.657$). All recurrent patients underwent secondary cytoreduction at the time of first relapse and 32 (65.3%) of them were conservatively re-treated. Patients experiencing second and third relapse were 16 and 5, respectively. Median times from first to second, and from second to third relapse were, respectively, 22.5 months (IQR range 11–38 months) and 36 months (IQR range 10.5–169 months). Details regarding disease recurrence(s) are presented in Table 3.

At the time of relapse, all patients but three presented with the same pathologic findings as at first diagnosis. All these three patients had an initial diagnosis of serous BOT with non-invasive implants: one was diagnosed with invasive implants at her second relapse, 25 months from the first recurrence; the remaining two were diagnosed with low-grade serous ovarian carcinoma limited to the ovary 10 and 34 months from primary cytoreduction.

At univariable analysis, comparing patients who developed a recurrence ($N = 49$) vs. patients who did not ($N = 42$), the following variables were significant predictors of relapse: size of largest extra-ovarian lesion, PCI, completeness of cytoreduction, type of implants (Table 4). Three out of 5 patients with CC =2, however, showed long lasting progression-free interval (102, 141 and 190 months).

Table 1
Patient-, tumor- and treatment-related characteristics.

Variable	$N = 91$
Age (years), median [IQR]	31 [26–36]
BMI (kg/m^2), median [IQR]	22.5 [21–27.7]
Previous pregnancy, n (%)	
Yes	28 (30.8)
No	57 (62.6)
Missing	6 (6.6)
Preoperative serum CA125 levels (U/mL), median [IQR]	112 [32.2–346.7]
Diameter (cm) of the largest ovarian tumor, median [IQR]	7.5 [5.7–11]
Diameter (cm) of the largest ovarian tumor, n (%)	
<5	9 (9.9)
5–9	36 (39.5)
10–15	15 (16.5)
>15	6 (6.6)
Missing	25 (27.4)
Bilateral ovarian involvement, n (%)	
No	55 (60.4)
Yes	36 (39.6)
Number of extra-ovarian lesions per patient, median [IQR]	3 [1–7]
Number of extra-ovarian lesions per patient, n (%)	
<5	54 (59.3)
5–9	21 (23.1)
10–15	9 (9.9)
>15	7 (7.7)
Size (mm) of largest extra-ovarian lesion, median [IQR]	10 [5–10]
Peritoneal cancer index, median [IQR]	3 [2–5]
Surgical approach, n (%)	
Laparoscopic/robotic	38 (41.8)
Open	53 (58.2)
Completeness of cytoreduction, n (%)	
0 (no visible residual tumor)	83 (91.2)
1 (residual nodules ≤0.25 cm)	3 (3.3)
2 (residual nodules >0.25 cm and ≤ 2.5 cm)	5 (5.5)
3 (residual nodules >2.5 cm)	0 (0)
Post-operative complications, n (%)	
G 1–2	1 (1.1)
G 3–4	2 (2.2)
G 5	0 (0)
FIGO stage, n (%)	
IIA	5 (5.5)
IIB	35 (38.4)
IIIA	8 (8.8)
IIIB	36 (39.5)
IIIC	7 (7.7)
Implants, n (%)	
Non-invasive	78 (85.7)
Invasive	13 (14.3)
Adjuvant therapy after surgery n (%)	
None	73 (80.2)
Chemotherapy	13 (14.2)
Hormone therapy	4 (4.4)
Chemotherapy followed by hormone therapy	1 (1.1)

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; G, grade; IQR, interquartile range.

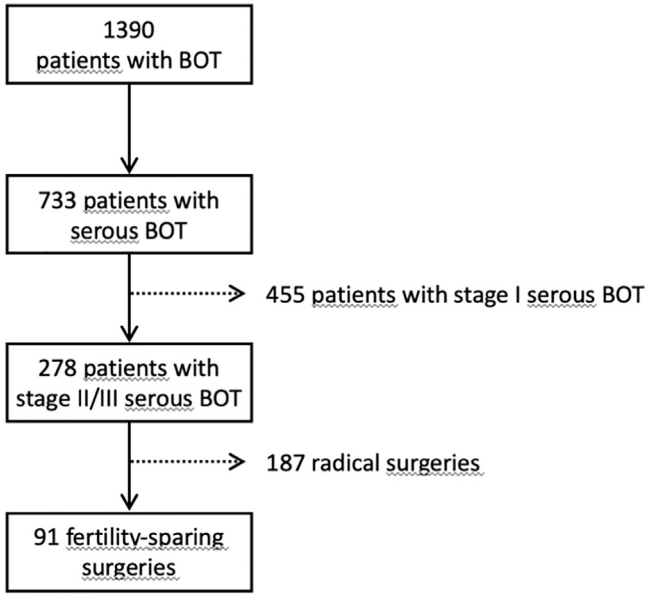

Fig. 1. Study cohort.

Table 2
Surgical procedures performed at the time of primary cytoreductive surgery.

Surgical procedures, n (%)	N = 91
Unilateral	
Ovarian cystectomy	19 (20.9)
Salpingo-oophorectomy	31 (34.1)
Bilateral	
Ovarian cystectomy	6 (6.6)
Salpingo-oophorectomy	5 (5.5)
Salpingo-oophorectomy and contralateral cystectomy	30 (32.9)
Removal of uterine implant(s)	9 (9.9)
Appendectomy	25 (27.4)
Lymphadenectomy	
Pelvic	15 (16.4)
Para-aortic	9 (9.9)
Omentectomy	83 (91.2)
Peritonectomy	
Pelvic	75 (82.4)
Broad ligament	8 (8.8)
Ovarian fossa	33 (36.2)
Pouch of Douglas	32 (35.1)
Vesico-uterine fold	13 (14.2)
Abdominal	22 (24.1)
Paracolic gutter	17 (18.7)
Diaphragm	10 (10.9)
Rectal or sigmoid colon serosal shaving	12 (13.1)
Large bowel serosal shaving (other than recto-sigmoid)	1 (1.1)
Endometrial biopsy(ies)	3 (3.3)
Random peritoneal biopsy(ies)	28 (30.7)

Table 3
Oncologic and reproductive outcomes.

Oncologic outcomes	
Patients experiencing relapse, n (%)	49 (53.8)
Time (months) from the surgery to 1st relapse, median [IQR]	22 [9.5–57]
Site of 1st relapse[a], n (%)	
Ovary(ies)	37 (75.5)
Uterus	1 (2)
Pelvic peritoneum	14 (28.5)
Abdominal peritoneum	6 (12.2)
Abdominal wall	1 (2)
Treatment of 1st relapse, n (%)	
Surgery	49 (100)
Still conservative	32 (65.3)
Non conservative	17 (34.7)
Chemotherapy	
Exclusive	0 (0)
Adjuvant	6 (12.2)
Hormone therapy	
Adjuvant	1 (2)
Patients experiencing 2nd relapse, n (%)	16 (32.6)
Time (months) from the 1st to 2nd relapse, median [IQR]	22.5 [11–38]
Site of 2nd relapse[a]	
Ovary(ies)	9 (56.2)
Uterus	2 (12.5)
Pelvic peritoneum	8 (50)
Abdominal peritoneum	6 (37.5)
Treatment of 2nd relapse, n (%)	
Surgery	14 (87.5)
Still conservative	10 (62.5)
Non conservative	4 (25)
Chemotherapy	
Exclusive	2 (12.5)
Adjuvant	5 (31.2)
Hormone therapy	
Adjuvant	0 (0)
Patients experiencing 3rd relapse, n (%)	5 (10.2)
Time (months) from the 2nd to 3rd relapse, median [IQR]	36 [10.5–169]
Site of 3rd relapse[a]	
Ovary(ies)	3 (60)
Pelvic peritoneum	2 (40)
Abdominal peritoneum	1 (20)
Treatment of 3rd relapse, n (%)	
Surgery	5 (100)
Still conservative	4 (80)
Non conservative	1 (20)
Chemotherapy	
Exclusive	0 (0)
Adjuvant	1 (20)
Hormone therapy	
Adjuvant	0 (0)
Follow-up (months), median [IQR]	127 [91–179]
Status at last follow-up, n (%)	
NED	88 (96.7)
AWD	2 (2.2)
DOD	1 (1.1)
Reproductive outcomes	
Patients attempting to conceive, n (%)	29 (31.8)
Pregnancy, n	24
NFTD	22
SFTM	2

AWD, alive with disease; DOD, dead of disease; IQR, interquartile range; NED, no evidence of disease; NFTD, normal full-term delivery; SFTM, spontaneous first-trimester miscarriage.
[a] More than one site could be involved in the same patient.

After multivariable adjustment for possible confounders, the size of extra-ovarian lesions and the presence of invasive implants resulted as the only independent predictors of recurrence (Table 4).

The Kaplan–Meier curves for DFS and DSS are presented in Fig. 2. Median DFS of the entire patient cohort was 96 months (95% CI, 24.6–167.3). Recurrences followed a linear time pattern and three-, five-, and ten-year DFS rates were 64.8%, 58.2%, and 46.1%, respectively. Median DSS was not reached. The only case of death occurred in a patient presenting with stage II and non-invasive implants at initial diagnosis. This patient underwent surgery achieving macroscopic complete cytoreduction and received post-operative (combination platinum-based) chemotherapy. She first recurred 19 months after primary surgery, and died from serous BOT with non-invasive implants after 32 months from first relapse.

Twenty-nine patients (31.8%) attempted to conceive. Twenty (68.9%) of them achieved at least one pregnancy and 18 (62%) gave birth at least to a healthy child. In total, 22 live births were reported, 4 women having 2 full-term pregnancies (Table 3). Nine patients (31%) underwent ART: 6 of these had at least one live born infant, and 3 had no pregnancies. In particular, only 1 out of the 5 patients conservatively treated with bilateral salpingo-oophorectomy and uterine preservation underwent ART. She achieved one pregnancy giving birth to a healthy child. Six out of the 20 (30%) recurrent patients re-treated conservatively achieved at least one pregnancy giving birth to a healthy child. No significant differences in the pregnancy nor live birth rates were observed in patients undergoing open versus minimally invasive surgery.

After completion of childbearing, none of our patients underwent the so-called *completion surgery*, including resection of the uterus and the (eventual) remaining ovary.

At the end of the observation period, 88 patients (96.7%) showed no evidence of disease, 2 (2.2%) were alive with disease, and 1 patient (1.1%) experienced relapse and died from BOT.

4. Discussion

Experience with conservative treatment of advanced-stage serous BOTs is very limited, mostly due to the low frequency of such a diagnosis. Even though current international guidelines suggest that FSS could be considered in selected patients with stage II or III serous BOTs [5,6], there is still a need for factors able to adequately predict the risk of treatment failure. Furthermore, the incidence of frankly malignant relapses has not been yet clearly estimated.

The present study, conducted among oncological referral centres, members of the main gynecologic oncology Italian cooperative group, reports on the largest series of patients undergoing FSS for stage II – III serous BOT.

After a median follow-up of about 10 years, 53.8% of patients experienced a relapse, with a rate of recurrence under the form of frankly

Table 4
Univariable and multivariable Cox regression analysis of factors predicting recurrence.

Univariable analysis			
Variable	Recurrence NO N = 42	Recurrence YES N = 49	*p*-Value
Age (years), median [IQR]	33 [28–36.7]	30 [24.2–34]	0.078
BMI (kg/m^2), median [IQR]	23.5 [21.4–29.6]	22.4 [20.2–26.8]	0.187
Preoperative serum CA125 levels (U/mL), median [IQR]	64 [31−313]	140 [35–349]	0.315
Diameter (cm) of the largest ovarian cyst, median [IQR]	8 [6–10.7]	7 [5–11.5]	0.611
Bilateral ovarian involvement, n (%)			0.552
No	24 (57.1)	31 (63.3)	
Yes	18 (42.9)	18 (36.7)	
Surgical management of ovarian lesion(s), n (%)			0.092
Cystectomy	7 (16.7)	18 (36.7)	
Salpingo-oophorectomy	20 (47.6)	16 (32.7)	
Salpingo-oophorectomy and contralateral cystectomy	15 (35.7)	15 (30.6)	
Number of extra-ovarian lesions per patient, median [IQR]	3 [1–6.5]	3 [1–7]	0.656
Size (mm) of largest extra-ovarian lesion, median [IQR]	6.5 [4–10]	10 [5–15]	0.006
Peritoneal cancer index, median [IQR]	2 [1–4.2]	4 [2–5]	0.028
Surgical approach, n (%)			0.131
Laparoscopic/robotic	14 (33.3)	24 (49)	
Open	28 (66.7)	25 (51)	
Tumor residual after surgery			0.046
No	41 (97.6)	42 (85.7)	
Yes	1 (2.4)	7 (14.3)	
FIGO stage, n %			0.282
II	21 (50)	19 (38.8)	
III	21 (50)	30 (61.2)	
Implants			0.016
Non-invasive	40 (95.2)	38 (77.6)	
Invasive	2 (4.8)	11 (22.4)	
Pregnancy after surgery			0.532
No	34 (81)	37 (75.5)	
Yes	8 (19)	12 (24.5)	
Adjuvant chemotherapy after surgery			0.394
No	37 (88.1)	40 (81.6)	
Yes	5 (11.9)	9 (18.4)	

Multivariable Cox regression analysis		
Variable	N = 91	
	HR [95% CI]	*p*-Value
Size of largest extra-ovarian lesion *(1 mm increase from median diameter)*	1.02 [1.00–1.04]	0.018
Peritoneal cancer index *(1 point increase from median diameter)*	0.98 [0.86–1.12]	0.812
No residual tumor after surgery *(vs. yes)*	0.87 [0.26–2.83]	0.820
Non-invasive implants *(vs. invasive)*	0.46 [0.23–0.92]	0.028

BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IQR, interquartile range.

invasive carcinoma of 2.2%. The size of extra-ovarian lesions and the presence of invasive implants were the only independent predictors of recurrence.

To date, excluding anecdotal case reports, only 130 advanced-stage serous BOT patients have been reported in the literature as having received FSS, mostly from small institutional series [8–13]. The only further large retrospective study, including 65 cases, has been published very recently by Gouy et al. [8]. Wide variations in the incidence of relapse have been reported after FSS for stage II – III serous BOT, with rates ranging from 25% to 60% [8–13]. The recurrence rate observed in our patients (53.8%) is similar to that reported by Gouy et al. (58.4%), while the risk of progression to malignant disease in our patients seems to be lower (2.2%) than that observed by these authors (12%) in spite of the longer median follow-up (10.5 vs 6.1 years). The rate of invasive transformation seen in our series is, however, consistent with that reported in the literature (2–3%) for all BOTs [4,14].

It has been estimated that, regardless of disease stage, the risk for recurrence increases up to 3 fold after FSS [4]. Such risk appears to be higher in patients with extra-ovarian disease [6,7].

Despite the risk of relapse associated with a conservative management, the safety of FSS is supported by the overall data available on BOTs, showing that the large majority of recurrences are in form of borderline lesions, readily curable with further surgery with a favourable prognosis [4,6,14,15]. In our series, all recurrent patients but one (48/49, 97.9%) are still alive at the time of the present analysis. Moreover, the overall 5-year survival rate (98.9%) in our study seems to be superimposable to those reported in the largest series of advanced-stage serous BOT patients treated with radical surgery (ranging from 91% to 98%) [9,19].

Only a small minority (10–15%) of BOTs with extra-ovarian disease has invasive implants [4,9,20]. Data on conservative treatment of BOTs with invasive implants are even more limited than those available for tumors with extra-ovarian non-invasive disease. The presence of invasive implants seems to be associated with a less favourable prognosis, with higher risks of recurrence and malignant transformation, and shorter disease-free interval than those observed for tumors with non-invasive implants. So far, less than 30 conservative treatments have been reported in the literature for BOTs with invasive implants

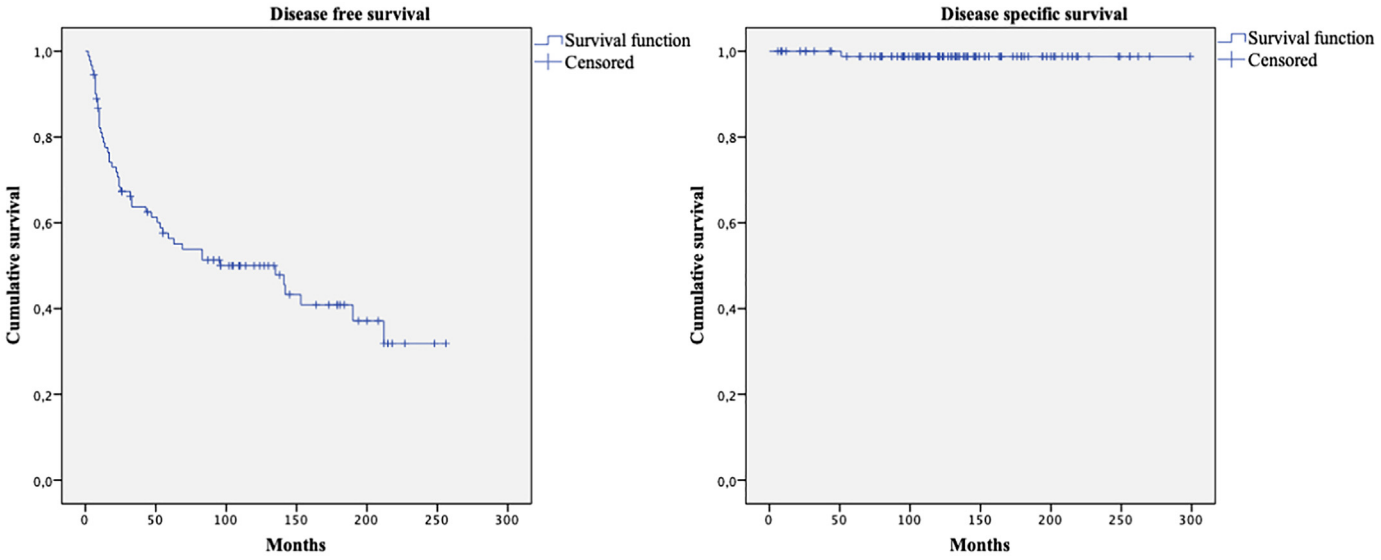

Fig. 2. Kaplan–Meier curves for disease-free survival (DFS) and disease-specific survival (DSS).

[8,11,12,15,21,22]. In the present study, multivariable analysis showed invasive implants as independent predictor of recurrence, confirming their prognostic importance also in a fertility-sparing setting.

None of them, however, relapsed as frankly invasive carcinoma, and there was no evidence of a significantly different time to first relapse when compared with non-invasive implants. Moreover, the presence of invasive implants showed no impact on DSS, with the only one death occurring in a patient with non-invasive implants. These data, however, are still controversial and the prognostic impact of the implants pattern could be substantially affected by the low numbers and pathological interpretation.

The presence of extra-pelvic vs. pelvic only peritoneal implants (stage III vs. stage II) would not significantly affect the recurrence rate in serous BOTs [23,24]. Our study confirmed these data. Multivariable analysis showed the size of peritoneal lesions, but not the stage of disease, neither the PCI, as independent predictor of recurrence. It is to note that PCI is a quantitative score combining the abdominal distribution of the tumor with the size of lesions. We found the PCI to be correlated with the recurrence risk at univariable analysis ($p = 0.028$); such statistical significance, however, was lost after multivariable adjustment ($p = 0.812$). These figures suggest that the extra-ovarian tumor load rather than the dissemination pattern has a role in determining the disease outcome in this setting of patients.

Cytoreductive surgery is recommended in BOTs with peritoneal implants [5,6]. In this respect, it has to be considered that, in our series, tumor residual correlated with risk of recurrence at univariable ($p = 0.046$) without achieving statistical significance at multivariable analysis ($p = 0.82$).

The low number of patients with residual disease is likely a plausible explanation for such result. The long-lasting progression-free intervals observed in some patients with residual disease must be, however, taken into consideration. The risk for progression in small peritoneal implants is probably very low [23], and a case report suggested that some of them could regress spontaneously after the removal of the ovarian tumor [25]. In our study, all women undergoing adjuvant chemotherapy relapsed, regardless the presence of residual disease and/or invasive implants. To date, the benefit of postoperative chemotherapy has not been demonstrated for advanced-stage BOTs. A meta-analysis including 181 BOTs with invasive implants from 26 studies concluded that there is no evidence for supporting adjuvant therapy even in the presence of invasive implants [26]. Thus, cytoreductive surgery still remains the cornerstone of treatment in BOTs with peritoneal implants, and all attempts should be made during surgery to achieve complete cytoreduction.

Several studies have shown an increased risk of recurrence after cystectomy instead of salpingo-oophorectomy [4,7]. In our series, the frequency of relapse was not significantly different among patients conservatively treated with cystectomy vs those undergoing salpingo-oophorectomy ($p = 0.092$), and this is true also in the presence of bilateral disease. Serous BOTs are reported as bilateral in 15–40% [3,14]. This is confirmed in our series with final pathology showing bilateral ovarian disease in 39.6%. Approximately one-third of our patients presented with both ovarian and extra-ovarian disease at the time of first relapse. Based on the above, in a context of FSS for advanced-stage serous BOT, the risk of recurrence would not seem to be related to the ovarian preservation per se, but to the natural history of the initial peritoneal spread. The low numbers in our series do not allow to draw any conclusion with respect to the reproductive outcomes in relation to the choice of ovarian surgery (cystectomy vs salpingo-oophorectomy) in case of bilateral disease. A randomized study, however, showed better reproductive outcomes without increasing the recurrence rate following bilateral cystectomy compared with unilateral adnexectomy plus contralateral cystectomy [27]. Based on these results, cystectomy should be now considered the preferable management for patients with bilateral BOTs regardless of extra-ovarian implants. Bilateral salpingo-oophorectomy with uterine preservation is a fertility-sparing option allowing a reasonable chance of reproductive success. It should be reserved, however, exclusively for patients with bilateral massive ovarian tumor for whom preservation of healthy ovarian tissue is not technically feasible [6,7].

The pregnancy outcome after FSS in advanced-stage serous BOT is much less known than its oncologic safety. In our study, considering only women who tried to conceive, pregnancy and live birth rates were 68.9% and 62%, respectively. These figures are very consistent with those reported by Gouy et al. (pregnancy rate: 68.9%; live birth rate: 58.6%) [8]. Since the achievement of pregnancy is the most important indicator of the success of a fertility-sparing treatment, the observed pregnancy and live birth rates represent a good result. It has been reported that patients with serous BOT frequently present with a previous history of infertility [28]. In our series, about one third of patients attempting to conceive underwent ART, with no cases of recurrence after ovarian stimulation and/or in vitro fertilization procedures. To date, only few authors have investigated the association between the use of fertility drugs and the risk of recurrence in BOTs, and they did not find any clear association [29–32]. The limited data available

do not allow to draw definitive conclusions on the safety of ART in patients with advanced-stage serous BOTs. In the light of the considerations above, however, we believe that early referral for reproductive counselling should be mandatory in order to maximize the likelihood of a live birth.

In our series, the median time from primary cytoreduction to first relapse (22 months) seems to be in line with that seen in several studies showing that most recurrences occur during the first 2 years of follow-up [7]. Such time interval could sometimes be insufficient to allow childbearing before further surgery, and repeated fertility-sparing procedures should be considered. Fifty-seven percent of our relapses occurred within the first 2 years from primary cytoreduction. The majority (71.4%) were re-treated by FSS, allowing at least one successful pregnancy in one third of them.

The retrospective setting, the long study period, and the use of different adjuvant strategies represent the main limitations of our study. Moreover, in spite of the uniform criteria adopted, the pathological review was not centralized but performed by different institutionally dedicated pathologists. Nevertheless, the present study reports on the largest series of advanced-stage serous BOTs selected for fertility preservation with the longest median follow-up time.

In conclusion, advanced-stage serous BOTs can be safely selected for fertility-preservation management. Despite the high rate of recurrence, FSS provides good chances of a reproductive success without a negative impact on overall survival. Complete cytoreduction seems to be of primary importance while the role of adjuvant treatment is still to be defined. The presence of invasive peritoneal implants affects the disease-free outcome with no impact on overall survival nor reproductive outcome. The risk of recurrence would not seem to be related to the ovarian preservation per se, but to the natural history of the initial peritoneal spread. In this respect, a better knowledge of the biomolecular characteristics of peritoneal disease is warranted.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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