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Fertility sparing surgery in patients with advanced borderline ovarian tumors: Oncologic outcomes of a single-institution cohort

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HIGHLIGHTS

- 86 patients with advanced BOTs treated with FSS were included in this large single-center retrospective series.
- After a median follow-up of more than 15 years, 76.7 % of patients experienced at least one recurrence.
- Most recurrences occurred in the ovaries, with no impact on survival. Only one patient died from tumor progression.
- Invasive implants were not confirmed to be associated with higher recurrence rates.
- Despite high recurrence rates, every effort should be made to preserve fertility in young women with advanced BOTs.

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ABSTRACT

Introduction. The purpose of this single-center retrospective analysis is to evaluate the long-term feasibility and oncologic safety of fertility-sparing surgery (FSS) in patients with advanced borderline ovarian tumors (BOTs).

Methods. Patients with FIGO stage IIA-IIIC BOTs treated with FSS between 1985 and 2021 were evaluated.

Results. A total of 86 patients were included, the majority having serous histology (90.7 %), bilateral ovarian involvement (61.6 %), and stage III disease (54.6 %) with non-invasive implants (80.2 %). The most common surgical approach was unilateral adnexectomy with/without contralateral cystectomy (58.1 %)
After a median follow-up of 182 months, 66 patients (76,7 %) experienced recurrence, with a median RFS of 148 months; among them, 36 relapsed more than once. Most patients experienced isolated ovarian recurrence at both first (69.7 %) and second relapse (60.0 %); in these patients, a rechallenge with FSS was offered in most cases, whereas radical surgery was preferred (53.3 %) at third recurrence. Three patients with recurrent disease developed invasive low-grade serous ovarian carcinoma (LGSOC). At univariable analysis, the laterality of ovarian involvement ($p = 0.027$) and the type of adnexal procedure ($p = 0.019$) were significant predictors of recurrence. At last follow-up 83 patients (96.5 %) were alive without evidence of disease, 2 patients (2.3 %) were alive with persistent/recurrent disease and death occurred in only one patient (1.2 %).

Conclusions. Despite the high recurrence rate, our series demonstrates that FSS has excellent oncologic outcomes in managing advanced BOTs. Therefore, fertility preservation is advised in young women with advanced BOTs who have not yet fulfilled their desire for childbearing.

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1. Introduction

Borderline ovarian tumors (BOTs) account for 10–20 % of all ovarian neoplasms and represent a unique entity with different pathologic and clinical features compared to ovarian malignant carcinoma.

Compared to their malignant counterparts, BOTs develop in younger patients and have a much better prognosis, even when extra-ovarian disease is detected [1]. The median age of diagnosis of BOTs is 40 years and about half of the cases are diagnosed in patients with childbearing desire, with excellent oncologic outcomes. The recently published ESGO-ESHRE-ESGE 2024 Guidelines for fertility-sparing surgery (FSS) in patients with ovarian cancer state that FSS should be considered in all fertile patients with a diagnosis of BOT, regardless of the stage, provided that invasive implants are excluded [2].

However, while robust evidence supports FSS in patients with early-stage disease [3,4], the oncologic safety and the fertility outcomes of FSS in patients with advanced BOTs are still debated [4–11].

Additionally, although the 2019 ESMO–ESGO consensus conference recommendations on ovarian cancer differentiate BOTs with invasive extra-ovarian implants from low-grade ovarian carcinoma (LGSOC), the 2024 ESGO-ESHRE-ESGE Guidelines group BOTs with invasive implants together with LGSOC and exclude the possibility of FSS for these patients, further complicating the decision-making process in this scenario [2].

The purpose of this single-center retrospective analysis is to evaluate the long-term oncologic safety of FSS in patients with advanced BOTs, with the hope of drawing a reliable picture of BOTs' management in a tertiary gynecologic oncology referral center and providing further evidence to evaluate the feasibility of FSS in this setting.

2. Materials and methods

2.1. Study design

This is a single-institution retrospective study with the primary objective of evaluating the oncologic outcomes in patients treated with FSS for FIGO stage IIA-IIIC BOTs in a high-volume gynecologic oncology center. Primary endpoints were Recurrence-Free Survival (RFS), defined as the time from primary surgery to first recurrence or censoring, and Overall Survival (OS), defined as the time from primary surgery to death or censoring. Secondary endpoint was identification of predictive factors of recurrence.

2.2. Study population

Patients included in this series were referred to our institution for FSSfrom 1st January 1985 to 31st December 2021. The following inclusion criteria were considered for patients' selection: a) histologically proven newly-diagnosed FIGO stage IIA-IIIC serous, sero-mucinous, and mucinous BOTs; 2) age < 45 years; 3) desire for fertility preservation, as assessed during preoperative work-up. Surgical treatment was considered fertility-sparing if at least the uterus and part of one ovary were preserved. Patients treated elsewhere who were referred to our institution for follow-up only were excluded from this analysis.

All cases were evaluated by the dedicated pathologists of our Institution. Tumor stage was defined according to the FIGO 2014 classification [12] and all cases diagnosed before 2014 were re-staged consequently. Despite the 2014 WHO classification [13] states to consider BOTs with extra-ovarian invasive implants as “extra-ovarian low-grade serous ovarian carcinoma”, the 2019 ESMO–ESGO consensus conference recommendations on ovarian cancer do not support this terminology [14]. Therefore, we included in our analysis patients with BOTs with both non-invasive and invasive extra-ovarian implants.

Patients' demographic, clinical, and pathological data were collected from internal electronic records. Tumor-related data included histology, the type of extra-ovarian implants (invasive vs non-invasive), the laterality of ovarian involvement, tumor stage, and the tumor intra-abdominal extension assessed with the Peritoneal Cancer Index (PCI) [15]. Since microinvasion and micropapillary patterns were reported starting from the early 2000s and were not available for almost half of our cohort, these pathologic features were excluded from this analysis.

Among the recorded treatment-related variables were residual disease (RD) at primary surgery was defined as follows: i) R0 if complete resection was achieved; ii) R1 in case of RD < 1 cm; iii) R2 in case of RD > 1 cm.

Administration of adjuvant chemotherapy was considered on a case-by-case basis, and was typically proposed for patients with RD after surgery, peritoneal invasive implants, or a micropapillary growth pattern.

Follow-up included gynecological examination, ultrasound, and tumor marker assessments every 3–4 months during the first 2 years, and every 6 months thereafter. Abdominal CT scan and/or MRI were performed annually.

In case of suspected recurrence, an abdominal CT scan or MRI was used to confirm and stage the disease. For cases of small-volume, non-univocal, suspected isolated ovarian recurrence, a watchful ultrasound follow-up was indicated until unequivocal confirmation of disease. In case of suspected recurrence but inconclusive imaging findings, a diagnostic laparoscopy was offered in selected cases. Surgical intervention with cytoreductive intent was indicated upon confirmation of unequivocal disease recurrence.

All recurrences were registered as assessed in each patient's clinical electronic records. For each recurrence, the timing, site of relapse, and administered treatment were recorded.

2.3. Statistical analysis

Discrete variables were expressed in percentages and compared using Fisher's Exact or Chi-Square Test. Continuous variables were expressed as medians and compared using the Sum-Rank-Test.

Logistic regression models were used to evaluate the impact of different covariates on the incidence of complications.

All statistical tests were two-sided. *Stata software 9.0* was used to perform all statistical analyses. A level of $p < 0.05$ was adopted for significance.

3. Results

3.1. Study population, pathology and treatment

86 patients with FIGO stage IIA-IIIC BOTs referred to our institution for primary surgical treatment from 1st January 1988 to 31st December 2021 were included in the study.

Table 1 reports patients' baseline characteristics. The median age at diagnosis was 29, and all patients had a favorable ASA score and good performance status. The median CA125 at diagnosis was 155 U/mL and most of the cases (61.6 %) had bilateral ovarian involvement at diagnosis. 78 (90.7 %) patients were diagnosed with serous BOTs, whereas mucinous and sero-mucinous histology was found in 5 (5.8 %) and 3 (3.5 %) patients, respectively. Most patients had FIGO stage III disease and non-invasive implants at final pathology: stage IIA disease was found in 6 (7.0 %) patients, stage IIB in 33 (38.4 %), and stage IIIA, IIIB, and IIIC in 27 (31.4 %), 12 (13.9 %) and 8 (9.3 %) patients, respectively. Concerning extra-ovarian disease, 69 (80.2 %) patients had peritoneal non-invasive implants, whereas invasive implants were found in 17 (19.8 %) patients. The median PCI was 1,5 (IQR 1–2, range 1–10).

61 patients (70.9 %) received open surgery, and 25 (29.1 %) received laparoscopy. Table 2 reports the surgical staging and cytoreductive procedures performed. Unilateral adnexectomy with or without contralateral cystectomy was the preferred surgical procedure. 22 (25.6 %) patients underwent unilateral adnexectomy and 28 patients (32.5 %) received unilateral adnexectomy with contralateral cystectomy. Preservation of both ovaries was feasible in the remaining 36 (41.9 %) patients, of

Table 1
Clinical and pathologic baseline characteristics of patients.

		N	% / IQR
Age	Median	29	25–33
BMI	Median	21.5	19.9–24.0
CA125	Median	155	57.6–397.0
PCI	Median	1,5	1–2
	Range	1–10	–
Ovarian involvement	Unilateral	33	38.4
	Bilateral	53	61.6
Histology	Serous	78	90.7
	Mucinous	5	5.8
	Seromucinous	3	3.5
Citology	Positive	22	25.6
	Negative	36	41.9
	NA	28	32.5
FIGO Stage	IIA	6	7.0
	IIB	33	38.4
	IIIA	27	31.4
	IIIB	12	13.9
	IIIC	8	9.3
Peritoneal implants	Non-invasive	69	80.2
	Invasive	17	19.8

whom 11 (12.8 %) received unilateral ovarian cystectomy and 25 (29.1 %) underwent bilateral ovarian cystectomy.

R0 was achieved in 75 (87.2 %) of patients, whereas 10 (11.6 %) and 1 (1.2 %) had R1 and R2 at the end of surgery, respectively. Comprehensively, 85 (98.8 %) patients received optimal (RD < 1 cm) cytoreduction (Table S1).

Adjuvant chemotherapy after surgical treatment was administered in 23 (26.7 %) patients. Of these, 21 received platinum-based monotherapy, whereas only 2 received platinum-based combination chemotherapy (Table S2). Administration of adjuvant chemotherapy was more frequent in patients with invasive implants: 12 patients out of 17 (70.6 %) with invasive implants received adjuvant chemotherapy, compared to 11 out of 63 (17.4 %) with non-invasive implants ($p < 0.0001$).

Table 2
Primary treatment procedures.

		N	%
Adnexal procedure	Unilateral cystectomy	11	12.8
	Bilateral cystectomy	25	29.1
	Unilateral adnexectomy	22	25.6
	Unilateral cystectomy + unilateral adnexectomy	28	32.5
Extra-ovarian staging/cytoreductive procedures	Omental biopsy	85	98.8
	Omentectomy	53	61.6
	Appendectomy	31	36.0
	Pelvic peritonectomy	29	33.7
	Upper abdomen peritonectomy	2	2.3
	Pelvic lymphadenectomy	7	8.1
	Para-aortic lymphadenectomy	2	2.3
	Recto-sigmoid shaving	5	5.8
	Small bowel shaving	1	1.2
	Large bowel shaving	1	1.2
	Recto-sigmoid resection	1	1.2
	Small bowel resection	0	0.0
	Large bowel resection	0	0.0
	Splenectomy	0	0.0
	Liver procedure	0	0.0
Surgical approach	LPS	25	29,1
	LPT	61	70,9
RD	R0	75	87,2
	R1	10	11,6
	R2	1	1,2
Adjuvant chemotherapy	No	63	73,3
	Yes	23	26,7
	Platinum-based monotherapy	21	91,3
	Platinum-based combination chemotherapy	2	8,7

3.2. Oncologic outcomes

The median follow-up was 182 months (IQR: 120–249 months). 66 patients (76.7 %) experienced at least one recurrence, with a median time to first relapse of 30 months (IQR 9–67). Median RFS was 148 months and RFS at 3, 5, 10, and 15 years was 87.8 %, 85.5 %, 71.1 %, and 55.7 %, respectively.

Most recurrences were local, with 60 (90.9 %) patients experiencing ovarian recurrence. Of these, 46 (69.7 %) patients developed isolated ovarian relapse, whereas 14 (23.3 %) patients experienced both ovarian and peritoneal recurrence. Pelvic implants at relapse were observed in 15 (22.7 %) patients, while extrapelvic and omental recurrence occurred in 2 (3 %) and 1 (1.5 %) patients, respectively. Isolated extra-ovarian recurrence occurred in 5 (7.6 %) patients.

Surgery was the treatment of choice in all patients at first recurrence. A rechallenge with FSS was offered in most cases (54; 81.8 %), with only 12 (18.2 %) patients receiving radical surgery with residual adnexectomy and concomitant total hysterectomy.

35 (40.7 %) and 15 (17.4 %) patients experienced a second and a third relapse, with a median time from the first to second relapse of 32 months (IQR 15.5–57) and a median time from the second to third relapse of 29 months (IQR 17.5–74). Similarly to the first recurrence, most of the recurrences were local at both the second and third relapse, with 30 (85.7 %) and 11 (73.3 %) patients experiencing ovarian recurrence, respectively. Isolated ovarian recurrence occurred in 21 (60.0 %) and 9 (60.0 %) patients at the second and third relapse, whereas isolated extra-ovarian relapse was observed at the second and third recurrence in 3 (8.6 %) and 3 (20.0 %) patients, respectively. As detailed in Table 3, the primary treatment at both the second and third recurrence was surgery in all but one patient. One patient experienced a progressive increase in CA125 levels fourteen years after FSS for relapsed BOT and a PET-CT scan revealed an isolated pelvic nodal recurrence;

Table 3
Anatomical and treatment characteristics of recurrences.

		N	%
1st relapse		66	76.7
Site	Ovary (ies)	60	90.9
	Isolated ovarian relapse	46	69.7
	Isolated extra-ovarian relapse	5	7.6
	Pelvic peritoneum	15	22.7
	Extrapelvic peritoneum	2	3.0
	Omentum	1	1.5
Treatment	Surgery	66	100
	Conservative surgery	54	81.8
	Radical surgery	12	18.2
	Adjuvant chemotherapy	2	3.9
2nd relapse		35	40.7
Site	Ovary (ies)	30	85.7
	Isolated ovarian relapse	21	60.0
	Isolated extra-ovarian relapse	3	8.6
	Pelvic peritoneum	9	25.7
	Extrapelvic peritoneum	3	8.6
	Pelvic nodes	1	2.8
Treatment	Surgery	34	97.1
	Conservative surgery	25	71.4
	Radical surgery	9	25.7
	Radiotherapy	1	2.9
	Adjuvant chemotherapy	1	2.9
3rd relapse		15	17.4
Site	Ovary (ies)	11	73.3
	Isolated ovarian relapse	9	60.0
	Isolated extra-ovarian relapse	3	20.0
	Pelvic peritoneum	3	20.0
	Mediastinum	1	6.7
	Vagina	1	6.7
Treatment	Surgery	14	93.3
	Conservative surgery	6	40.0
	Radical surgery	8	53.3
	Adjuvant chemotherapy	0	0
	Radiotherapy	1	6.7

however, the patient was not a candidate for surgical resection due to severe pelvic adhesions from prior surgeries and was successfully treated with external-beam radiotherapy. A second patient developed an isolated recto-vaginal septum recurrence following two relapses treated with radical surgery and subsequently received external-beam radiotherapy followed by vaginal brachytherapy with complete tumor regression.

FSS was still performed in most cases at the second recurrence, whereas more than half of the patients (53.3 %) underwent radical surgery at the third recurrence. As shown in Fig. 1, the choice for radical surgery gradually increased from the first to third recurrence, reflecting both clinicians' and patients' attitudes towards radical surgery with growing age and fulfillment of childbearing desire ($p = 0.008$).

Among patients who experienced at least one recurrence, all had the same pathological findings as their primary diagnosis, except for three patients diagnosed with LGSOC.

As shown in Table 4, at univariable analysis none of the prespecified variables were significantly associated with recurrence except for the laterality of ovarian involvement ($p = 0.027$) and the type of the adnexal procedure, with patients undergoing bilateral cystectomy experiencing a higher recurrence rate compared to those receiving unilateral cystectomy/adnexectomy or unilateral cystectomy with contralateral adnexectomy ($p = 0.019$).

Globally, 35 (40.7 %) patients underwent radical surgery, that was performed for recurrence in 29 patients or as completion surgery after fulfilling their desire for childbearing in 6 patients. The median time from diagnosis to radical surgery was 96 months (IQR 53–152), and the median age at radical surgery was 40 years (IQR 34–43). Among the 29 patients undergoing radical surgery for recurrent disease, only 3 patients experienced a further subsequent relapse ($p = 0.004$).

At last follow-up, 83 (96.5 %) patients were alive without evidence of disease, and 2 (2.3 %) patients were alive with persistent/recurrent disease. One patient (1.2 %) died of disease progression of serous BOT conditioning bowel obstruction after 11 years (133 months) from primary treatment.

4. Discussion

To the best of our knowledge, this is the largest single-center series of patients with advanced BOTs treated with FSS ever reported in the literature. We enrolled 86 patients with FIGO stage II–III BOTs who were treated with FSS, regardless of ovarian involvement, laterality, or the pathological features of extraovarian implants. After a median follow-up of more than 15 years, 76.7 % of patients experienced at least one recurrence, with a RFS rate at 5, 10 and 15 years of 85.5 %, 71.1 % and 55.7 %. Most recurrences occurred in the ovary/ovaries and were successfully managed surgically, with no significant impact on survival. Only one patient died from tumor progression, and 96.5 % of our cohort was alive without evidence of disease at the last follow-up.

Most BOTs develop in young fertile women who have not yet fulfilled their childbearing desire, thus raising the need for fertility-sparing therapeutic options that can provide good obstetrics outcomes without compromising oncologic safety.

In the literature, robust evidence exists about the excellent prognosis and fertility outcomes of patients with early-stage BOTs treated with FSS [3–5]. On the contrary, evidence regarding the feasibility of FSS in patients with advanced BOTs is limited, with only a few studies in the literature, most of which are small, single-institution retrospective series on a comprehensive total of approximately 250 patients [5–11].

The recurrence rate of advanced BOTs treated with FSS is highly variable in the literature and ranges from 25 % to 71 % [5–11]. Our data is similar to the recent single-center retrospective study of 65 patients published by Cang et al. [11], who reported a recurrence rate of 70.8 % after a median follow-up of 81.7 months. Conversely, it is slightly higher compared to the largest series on FSS in advanced BOTs reported by Falcone et al. [10] in the observational retrospective multicentric MITO-14 study. Among the 91 patients enrolled in their series, a recurrence rate of 53.8 % was observed, with a median time to first relapse of 22 months and a RFS rate at 3, 5 and 10 years of 64.8 %, 58.2 %, and 46.1 %, respectively. However, the median follow-up was shorter (127 months) and bilateral ovarian involvement was lower (39.6 %) compared to our series. Similarly, in a recent single-center study by Westermann et al. [4] reporting a recurrence rate of 40 % in 40 patients with advanced BOTs treated with FSS, the median follow-up period was notably shorter than ours (49 months).

According to the 2024 ESGO-ESHRE-ESGE Guidelines, FSS can be considered in all fertile patients with BOTs, regardless of the stage, provided that invasive extraovarian implants are not detected [2]. However, limited data in the literature support the worst prognostic impact of invasive implants in patients with advanced BOTs treated with

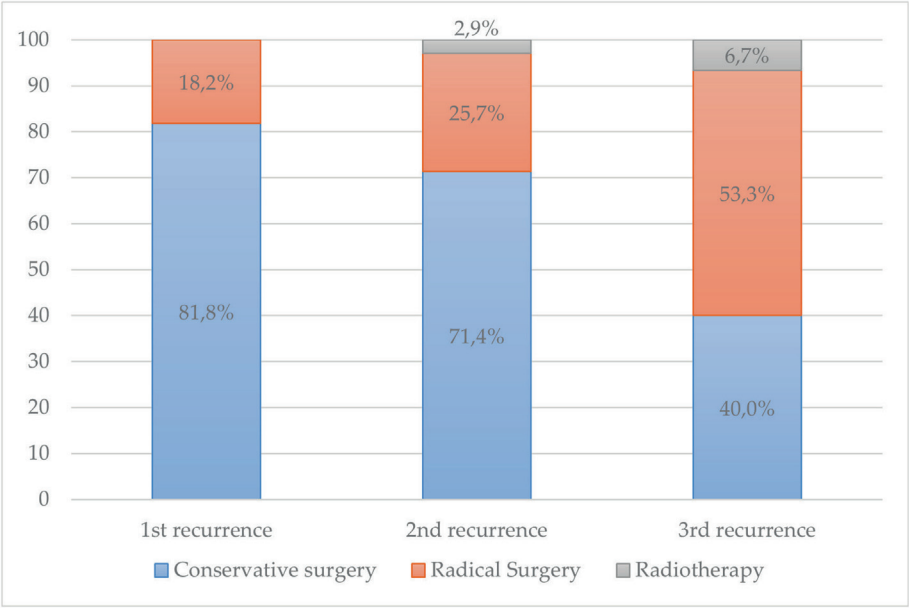

Fig. 1. Treatment choice at relapse.

Table 4
Predictors of recurrence.

Variable	Level	No recurrence	Recurrence	OR	95 % CI	*p* value
Age	continuous variable	–	–	0,99	0.90–1.09	0.888
CA125 level	continuous variable	–	–	1,00	1.00–1.00	0.542
Ovarian involvement	Unilateral (ref)	12 (36.3)	21 (63,6)	3,21	1.14–9.04	**0.027**
	Bilateral	8 (15.1)	45 (84.9)			
PCI	continuous variable	–	–	1,14	0.81–1.60	0.46
Surgical approach	Laparotomy (ref)	12 (19.7)	49 (80.3)	0,52	0.18–1.49	0.22
	Laparoscopy	8 (32)	17 (68)			
Ovarian procedure	Unilateral cystectomy	4 (36.4)	7 (63.6)	–	–	**0.019**
	Bilateral cystectomy	1 (4.0)	24 (96.0)			
	Unilateral adnexectomy	8 (36.4)	14 (63.6)			
	Unilateral adnexectomy + unilateral enucleation	7 (25.0)	21 (75.0)			
RD	0	20 (26.7)	55 (73.3)	–	–	0.134
	0–1	0 (0)	10 (100)			
	> 1	0 (0)	1 (100)			
Histology	Serous (ref)	17 (21.8)	61 (78.2)	0,54	0.12–2.45	0.42
	Non Serous	3 (37.5)	5 (62.5)			
Implants	Non invasive (ref)	18 (26.1)	51 (73.9)	1,40	0.45–4.36	0.56
	Invasive	2 (11.8)	15 (88.2)			
FIGO Stage	II (ref)	11 (28.3)	28 (71.7)	1,66	0.61–4.54	0.33
	III	9 (19.1)	38 (80.9)			
Adjuvant CT	Yes	4 (17.4)	19 (82.6)	1,62	0.48–5.47	0.54
	No (ref)	16 (25.4)	47 (74.6)			

FSS [4,10,11]. Additionally, no consensus currently exists on how invasive implants should be pathologically diagnosed, nor on how patients with invasive implants should be considered and clinically managed. In 2014, the WHO classification of gynecological tumors was revised, categorizing BOTs with peritoneal invasive implants as extraovarian metastatic LGSOC [13]. However, the 2019 ESMO–ESGO consensus conference on ovarian cancer did not accept this classification, maintaining the distinction between BOTs with invasive extraovarian implants and LGSOC, advocating the differing survival outcomes of patients with invasive implants compared to those with 'authentic' stage II or III LGSOC, as well as the distinct impact of adjuvant chemotherapy in LGSOC compared to BOTs with invasive implants [14].

Data on FSS in advanced BOTs with invasive implants is scarce. To date, approximately 30 patients have been reported in the literature regarding this issue, with inconclusive findings [5,8,10,11,16–18]. In the series by Gouy et al. [8], 65 patients with advanced BOTs treated with FSS were evaluated after a median follow-up of 6 years. The recurrence rate was 58 %, but no impact on DFS and OS was observed in the eight patients with invasive implants. In the series by Cang et al. [11], the presence of invasive implants in 9 patients was not associated with recurrence rate at univariate analysis [HR = 0.302 (95 %CI 0.034–2.639); p = 0,279], although it was significantly associated with shorter DFS at multivariate analysis. In the subanalysis of the MITO14 study [16] on 13 patients with invasive implants, recurrence rate was 84.6 % and no death occurred after a median follow-up of 146 months.

In our series, invasive implants were not associated with higher recurrence rates (OR 1.40; 95 %CI 0.45–4.36; $p = 0.56$). However, caution should be taken when interpreting our results. First, the limited number of cases with invasive implants may have impacted our findings. Second, administration of adjuvant chemotherapy was more frequent in patients with invasive implants, although adjuvant chemotherapy was not associated with improved recurrence rate at univariate analysis in our series (OR 1.62; 95 %CI 0.48–5.47) and the current literature does not support the utility of chemotherapy in patients with BOTs and invasive implants based on the results of a meta-analysis including 181 BOTs with invasive implants from 26 studies [19].

When dealing with FSS, the median time to first relapse and the timing of subsequent pregnancies are important issues. In our series, the median time from primary surgical treatment to first relapse was 30 months (IQR 9–67). Especially for patients of younger age, this time interval is relatively short, and most of them might develop recurrence before fulfilling their childbearing desire. While limited data exists on FFS for managing advanced BOTs, even less is available regarding its role in the management of recurrent disease [10,11]. In our series, the rate of patients re-treated with FSS at first recurrence was 81.8 %. More interestingly, among the 36 patients in our series who experienced a second relapse, 26 (71.4 %) underwent further FSS, and 6 out of 14 patients (40 %) received FSS for a third recurrence. The high rate of FSS rechallenge in our series is primarily attributed to the fact that most recurrences presented as isolated ovarian relapses, with only a minority of patients experiencing extra-ovarian recurrent disease. Globally, these findings and the excellent survival outcomes of our cohort suggest that, whenever surgically feasible, FSS in patients with both primary and recurrent disease should be encouraged, and radical surgery should be avoided until fulfillment of childbearing desire.

The step-wise evolution of both serous and mucinous tumors from BOTs to invasive carcinoma is well recognized. The rate of BOTs' progression of recurrent disease into LGSOC varies widely in the literature, ranges from 2 to 15 % [6–11,16,17,20–23], and is of particular concern in patients receiving FSS. In our series, among the 66 patients who experienced at least one recurrence, only three patients were diagnosed with invasive LGSOC. Our data align with the series by Falcone et al. [10], who described two patients with a primary diagnosis of BOT with non-invasive implants relapsing as LGSOC. These findings and the excellent survival outcomes of our cohorts suggest that, if invasive implants are considered a pathologically different entity from LGSOC, the truly malignant recurrence rate is low even after long follow-up periods.

The optimal surgical approach in FSS for BOTs is controversial. Minimally invasive surgery is the preferred surgical approach in patients with early-stage disease. However, concerns for inadequate exploration of the abdominal cavity, high tumor load, the gross appearance of ovarian masses resembling invasive carcinoma, and the risk of disseminating tumor cells via pneumoperitoneum likely explain why the preferred approach in most studies addressing FSS for advanced BOTs is open surgery. Similarly to other series, 70.9 % of patients in our population were treated with open surgery. However, in line with other cohorts and our previous findings on 535 FIGO Stage I-IV BOTs [3], the surgical approach did not influence recurrence, and laparoscopy was not associated with detrimental recurrence rates.

While surgical approach did not influence recurrence rates, our data show that the type of ovarian procedure is associated with recurrence. Patients who underwent bilateral cystectomy experienced a higher

recurrence rate compared to those undergoing unilateral cystectomy or adnexectomy or unilateral cystectomy with contralateral adnexectomy ($p = 0.019$).

In the literature, conflicting data address this topic. In the ambispective series of the AGO Study Group [23], unilateral salpingo-oophorectomy was associated with a 71 % increase in the risk of recurrence (HR 1.713; $p = 0.0155$) compared to bilateral adnexectomy and the highest risk was observed if cystectomy was performed with preservation of the primitively affected ovary (HR 5.662; $p < 0.0001$). In our previous series on 535 FIGO Stage I-IV BOTs, the adnexal surgical procedure was not associated with recurrence rate (p = 0,06). The 10-years recurrence rate was 23 % for unilateral adnexectomy and 31 % for unilateral cystectomy (p = 0,10) in patients with unilateral tumors, whereas it was 62 % for unilateral adnexectomy and contralateral cystectomy and 72 % for bilateral cystectomy (p = 0,35) in patients with bilateral ovarian involvement. In the metanalysis including 2752 patients receiving FSS for BOTs by Vasconcelos et al. [24], unilateral salpingo-oophorectomy was associated with decreased recurrence rate compared to cystectomy in the treatment of unilateral BOTs, whereas no significant difference between bilateral cystectomy and unilateral salpingo-oophorectomy with contralateral cystectomy (OR = 1.569) was observed among patients with bilateral ovarian involvement.

Comprehensively, all these data should be interpreted cautiously when compared to our cohort. Most studies addressing this issue include mainly early-stage BOTs. In advanced-stage disease, the extent of ovarian involvement plays a critical role in determining the type of adnexal procedure; a mono- or bilateral cystectomy is an option only if a sufficient amount of healthy ovarian tissue can be identified and to date there is no consensus on the preferred surgical adnexal procedure to be performed in these patients. The 2024 ESGO-ESHRE-ESGE Guidelines [2] state that bilateral ovarian cystectomy with macroscopic healthy ovarian tissue can be considered in bilateral BOTs, whereas unilateral adnexectomy and cystectomy are both acceptable strategies for unilateral BOTs. Our data show that bilateral cystectomy is associated with increased recurrence risk. However, given that most of relapses occur as BOTs in the ipsilateral and/or contralateral ovary and are successfully managed with salvage surgery with no overall survival effect, and that bilateral ovarian preservation might be associated with increased fertility outcomes, we believe that surgery should be personalized basing on pre- and intra-operative findings, provided that complete removal of adnexal disease is granted.

Complete cytoreduction is the goal of surgical treatment in patients with ovarian malignancies [25]. However, the impact of RD, the reasons for incomplete surgery, and the outcomes of patients with RD treated with adjuvant chemotherapy in advanced BOTs remain unclear. In the MITO-14 study [10] and the series by Gouy et al. [8], RD was reported in 8.8 % and 21.5 % of patients, respectively, and was not significantly associated with recurrence risk. However, neither study provided data on the location of RD, the reasons for incomplete surgery, or whether patients with RD were more likely to receive adjuvant chemotherapy. In contrast, the study by Cang et al. [11] reported RD in 23.3 % of patients and found a significant association with increased recurrence risk, both in univariate (HR 4.71) and multivariate analysis (HR 3.90). In our cohort, the incidence of RD was 12.8 %, and 73.3 % and 100 % of patients with R0 and R1–2 experienced disease recurrence, respectively, with no statistically significant difference ($p = 0.134$). No definitive conclusions can be drawn to explain these findings. First, it might be that the small number of patients with RD within our cohort impacted our findings. Second, 8 out of 11 patients with RD received adjuvant chemotherapy. Most of the patients with RD had miliary pelvic and extrapelvic peritoneal implants; however, all but one patient with RD experienced recurrence within the pelvis, with either isolated ovarian relapse or with concomitant pelvic peritoneum involvement. Although conclusive data on the role of adjuvant chemotherapy in this setting are lacking, it is possible that chemotherapy contributed to the regression of peritoneal implants, helping to achieve disease control and enabling a further FSS at recurrence. Additionally, all patients with RD in our cohort underwent complete resection of ovarian disease. The spontaneous regression of small peritoneal implants following the removal of ovarian disease has been reported in the literature [26,27]; this may explain the discrepancies observed between the initial sites of RD and the locations of disease recurrence in our cohort. Although further investigation is warranted, our findings support the possibility of offering carefully considered counseling on FSS, even in cases where complete resection of millimetric implants is not achievable.

The main limitations of this work are its retrospective nature and the long recruitment period, lasting more than 30 years, which might have led to selection biases. However, the main strengths of this work lie in the long follow-up of our cohort, lasting up to more than 20 years, and in its single-center design, granting homogeneity in pathologic evaluation, treatment choices and oncologic and obstetric monitoring in a referral hospital, and accounting for the largest single-center series to date on FSS in advanced BOTs.

5. Conclusions

Despite the high recurrence rate, our series demonstrates that FSS has excellent oncologic outcomes in the management of advanced BOTs and should not be reserved only for early-stage disease. Additionally, rechallenging with FSS in cases of recurrent disease appears feasible. Every effort should be made to preserve fertility in young women with advanced BOTs until they have fulfilled their childbearing desire.

Limited and inconclusive data exist regarding the feasibility of FSS in patients with invasive implants. Despite the small number of cases, our series suggests that FSS might be a viable option for these patients without compromising survival outcomes, provided they receive adequate counseling.

CRediT authorship contribution statement

Tommaso Bianchi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tommaso Grassi:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Elena De Ponti:** Writing – review & editing, Methodology, Formal analysis. **Marta Jaconi:** Writing – review & editing, Formal analysis. **Marta Seca:** Writing – review & editing, Data curation. **Alessandra Inzoli:** Writing – review & editing, Data curation. **Martina Bombelli:** Writing – review & editing, Data curation. **Giorgia Pecis Cavagna:** Writing – review & editing, Data curation. **Valeria Carazita:** Writing – review & editing, Data curation. **Daniela Giuliani:** Writing – review & editing, Data curation. **Stefania Chiari:** Writing – review & editing, Data curation. **Gaetano Trezzi:** Writing – review & editing, Data curation. **Alessandra Casiraghi:** Writing – review & editing, Data curation. **Andrea Alberto Lissoni:** Writing – review & editing, Supervision. **Robert Fruscio:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2025.06.009.

References

[1] A. du Bois, et al., Management of borderline ovarian tumors, Ann. Oncol. 27 (Apr. 2016) i20–i22, doi:10.1093/annonc/mdw090.

[2] P. Morice, et al., Fertility-sparing treatment and follow-up in patients with cervical cancer, ovarian cancer, and borderline ovarian tumours: guidelines from ESGO, ESHRE, and ESGE, Lancet Oncol. 25 (11) (Nov. 2024) e602–e610, doi:10.1016/S1470-2045(24)00262-6.

[3] M. Delle Marchette, et al., Oncologic and fertility impact of surgical approach for borderline ovarian tumours treated with fertility sparing surgery, Eur. J. Cancer 111 (2019), doi:10.1016/j.ejca.2019.01.021.

[4] T. Westermann, et al., Role of fertility-sparing surgery and further prognostic factors in borderline tumors of the ovary, Int. J. Gynecol. Cancer (Apr. 2024), doi:10.1136/ijgc-2023-005214 p. ijgc-2023-005214.

[5] G. Zanetta, et al., Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study, J. Clin. Oncol. 19 (10) (May 2001) 2658–2664, doi:10.1200/JCO.2001.19.10.2658.

[6] S. Camatte, et al., Fertility results after conservative treatment of advanced stage serous borderline tumour of the ovary, BJOG 109 (4) (Apr. 2002) 376–380, doi:10.1111/j.1471-0528.2002.01359.x.

[7] P. De Iaco, et al., Behaviour of ovarian tumors of low malignant potential treated with conservative surgery, Eu. J. Surg. Oncol. (EJSO) 35 (6) (Jun. 2009) 643–648, doi:10.1016/j.ejso.2008.09.011.

[8] S. Gouy, et al., Results after conservative surgery of stage II/III serous borderline ovarian tumors, Ann. Surg. Oncol. 28 (7) (Jul. 2021) 3597–3604, doi:10.1245/s10434-020-09250-7.

[9] C. Uzan, et al., Outcomes after conservative treatment of advanced-stage serous borderline tumors of the ovary, Ann. Oncol. 21 (1) (Jan. 2010) 55–60, doi:10.1093/annonc/mdp267.

[10] F. Falcone, et al., Fertility-sparing treatment in advanced-stage serous borderline ovarian tumors. An analysis from the MITO14 study database, Gynecol. Oncol. 161 (3) (2021) 825–831, doi:10.1016/j.ygyno.2021.03.023.

[11] W. Cang, et al., Oncological and reproductive outcomes after fertility-sparing surgery in patients with advanced-stage serous borderline ovarian tumor: a single-center retrospective study, J. Clin. Med. 12 (18) (Sep. 2023) 5827, doi:10.3390/jcm12185827.

[12] D.G. Mutch, J. Prat, 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer, Gynecol. Oncol. 133 (3) (Jun. 2014) 401–404, doi:10.1016/j.ygyno.2014.04.013.

[13] R.J. Kurman, et al., WHO Classification of Tumours of Female Reproductive Organs, 4th edition IARC, Lyon, 2014.

[14] N. Colombo, et al., ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease, Ann. Oncol. 30 (5) (May 2019) 672–705, doi:10.1093/annonc/mdz062.

[15] P. Jacquet, et al., Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis, 1996 359–374, doi:10.1007/978-1-4613-1247-5_23.

[16] F. Falcone, et al., Fertility-sparing treatment for serous borderline ovarian tumors with extra-ovarian invasive implants: analysis from the MITO14 study database, Gynecol. Oncol. 165 (2) (May 2022) 302–308, doi:10.1016/j.ygyno.2022.02.018.

[17] J. Prat, M. de Nictolis, Serous borderline tumors of the ovary, Am. J. Surg. Pathol. 26 (9) (Sep. 2002) 1111–1128, doi:10.1097/00000478-200209000-00002.

[18] L. Helpman, et al., Safety of ovarian conservation and fertility preservation in advanced borderline ovarian tumors, Fertil. Steril. 104 (1) (2015) 138–144, doi:10.1016/j.fertnstert.2015.03.038.

[19] I. Vasconcelos, et al., A Meta-analysis on the impact of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors with invasive implants, Oncologist 20 (2) (Feb. 2015) 151–158, doi:10.1634/theoncologist.2014-0144.

[20] D.M. Gershenson, et al., Serous borderline tumors of the ovary with noninvasive peritoneal implants, Cancer 83 (10) (Nov. 1998) 2157–2163, doi:10.1002/(SICI)1097-0142(19981115)83:10<2157::AID-CNCR14>3.0.CO;2-D.

[21] R. Vang, et al., Long-term behavior of serous borderline tumors subdivided into atypical proliferative tumors and noninvasive low-grade carcinomas, Am. J. Surg. Pathol. 41 (6) (Jun. 2017) 725–737, doi:10.1097/PAS.0000000000000824.

[22] D.M. Gershenson, et al., Ovarian serous borderline tumors with invasive peritoneal implants, Cancer 82 (6) (Mar. 1998) 1096–1103.

[23] A. du Bois, et al., Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) study group, Eur. J. Cancer 49 (8) (May. 2013) 1905–1914, doi:10.1016/j.ejca.2013.01.035.

[24] I. Vasconcelos, M. de Sousa Mendes, Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk, Eur. J. Cancer 51 (5) (Mar. 2015) 620–631, doi:10.1016/j.ejca.2015.01.004.

[25] A. Du Bois, et al., Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the arbeitsgemeinschaft gynaekologische onkologie studiengruppe ovarialkarzinom (AGO-OVAR) and the groupe d'Investigateurs nationaux pour les etudes des cancers de l'Ovaire (GINECO), Cancer 115 (6) (Mar. 2009) 1234–1244, doi:10.1002/cncr.24149.

[26] P. Morice, et al., Spontaneous regression of peritoneal implants in borderline ovarian tumor after salpingo-oophorectomy, J. Clin. Oncol. 21 (18) (2003), 3536e3538, doi:10.1200/JCO.2003.12.021.

[27] J. Delotte, et al., Spontaneous regression of peritoneal carcinomatosis in a borderline ovarian tumour, Eur. J. Obstet. Gynecol. Reprod. Biol. 142 (1) (2009) 84–85.