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Original Research

Oncologic and fertility impact of surgical approach for borderline ovarian tumours treated with fertility sparing surgery

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Abstract ***Background:*** Even if borderline ovarian tumours (BOTs) in young women treated with fertility-sparing treatment (FST) have an excellent outcome, the type of surgery might affect relapse and fertility. We investigated the effect of surgical approach (open surgery vs. laparoscopy) and type of surgery (salpingo-oophorectomy [SO] vs. cystectomy [Cy]) on oncologic and fertility outcomes in patients with BOT.
Patients and methods: Patients with BOT treated at San Gerardo Hospital, Monza, with FST in 1978–2013 period were included. Cox models, stratified by decade of surgery, were used to investigate the association between time to first recurrence or conception and clinical factors.
Results: Among 535 patients included, 271 underwent unilateral SO and 264 underwent Cy. Median follow-up was 13.5 years. Ten-year (10-yr) recurrence rate was 23% (95% confidence interval [CI]: 18–29%) for SO and 31% (95% CI: 24–38%) for Cy group ($P = 0.10$) in patients with unilateral tumour, whereas it was 62% (95% CI: 44–79%) and 72% (95% CI: 59–84%), respectively, ($P = 0.35$) in patients with bilateral tumour. Multivariable analysis showed no association between recurrence and surgical approach ($P = 0.44$), type of surgery ($P = 0.06$) and a negative association with advanced stage (hazard ratio [HR] = 3.18; 95%

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CI: 2.11–4.78; $P < 0.001$) and bilateral tumours (HR = 2.48; 95% CI: 1.78–3.47; $P < 0.001$). Among 252 patients (47.1%) with pregnancy desire, multivariable analysis showed no association between conception success and the type of surgery, surgical approach, histology and tumour laterality. Fertility after surgery was positively associated with prior pregnancy (HR = 1.68; 95% CI: 1.17–2.41; $P = 0.005$) and negatively associated with the number of surgical procedures (HR = 0.62; 95% CI: 0.53–0.73; $P < 0.001$).

Conclusions: The type of surgical procedures did not influence recurrence rate or fertility. However, additional surgical procedures decreased the fertility potential. These data can support clinicians in tailoring the best strategy for FST in young patients with BOT.

1. Background

The incidence of borderline ovarian tumour (BOT) is estimated between 2.5 and 5.5/100000 women every year [1,2], accounting for approximately 10–15% of all ovarian tumours. BOTs are a unique entity that differs from malignant epithelial ovarian cancer both from a pathological and a clinical point of view, with independent classification by the World Health Organisation (WHO) [3]. Compared with malignant tumours, BOT are more frequently diagnosed in premenopausal women, and approximately one-third of them are diagnosed before 40 years of age [2,4,5]. As the age of first pregnancy is constantly increasing in the last few decades [6], many women are diagnosed with BOT when their childbearing desire is not completed. In these patients, given the excellent oncological outcome reported for patients with early stage tumours, a fertility-sparing treatment (FST) is considered a valid treatment option. Many authors have demonstrated that FST does not worsen survival of patients with BOT, even if the risk of relapse might be increased [7]. However, there is no consensus about which surgical procedure should be performed to adequately treat these patients preserving their fertility. Some authors report higher rates of relapse in women undergoing cystectomy (Cy), thus advocating salpingo-oophorectomy (SO), whereas some others underline the potential decrease of fertility associated with the removal of one ovary [8]. In this retrospective analysis, we investigated the surgical factors associated with recurrence rate and fertility.

2. Patients and Methods

Consecutive patients with pathologically confirmed BOT treated at San Gerardo Hospital, Monza, between 1978 and 2013 were screened for inclusion in the analysis. All cases were reviewed by a dedicated pathologist and defined according to the WHO criteria [9]. Tumour stage was defined according to the 1987 International Federation of Gynecology and Obstetrics (FIGO) classification [3]. Peritoneal implants at first diagnosis and recurrence were defined as invasive or non-invasive, according to stromal peritoneal invasion. Inclusion criteria were primary surgery (or restaging surgery within 180 days) different from bilateral SO and preservation of the uterus. Patients younger than 18 years were excluded as they were followed up by paediatric oncologists.

The desire of pregnancy was verified by direct assessment at routine gynaecological follow-up visit or by phone interview. For all patients meeting the inclusion criteria, the association between recurrence and the type of surgery (SO vs. Cy), surgical approach (open surgery [open] vs. laparoscopy [LPS]) and other clinical factors were examined. The association between fertility, defined as the occurrence of at least one conception after surgery, and the same surgical and clinical variables was investigated. Patients with unknown or no desire for pregnancy or a diagnosis of primary sterility before surgery were excluded.

2.1. Treatment

Type of ovarian surgery was defined as SO (removal of the affected ovary and the ipsilateral fallopian tube with the conservation of the contralateral adnexa) or Cy. For patients with bilateral cysts, SO corresponded to unilateral SO + contralateral Cy and Cy to bilateral Cy. Laterality of tumour was considered for the oncologic outcomes analysis, whereas laterality of surgical procedures was considered for the fertility outcomes analysis, weighing the impact of any surgical resection of suspicious cysts even if benign. The cumulative incidence of recurrence, death and first pregnancy were separately estimated for bilateral tumours and surgical procedures. Additional surgical staging procedures, such as omentectomy, and peritoneal biopsies were also performed at diagnosis or during restaging surgery. Patients' follow-up included a gynaecological examination with transvaginal ultrasound and CA125 measurement every 3 months for the first 2 years and every 6 months afterwards.

2.2. Statistical analysis

The Kaplan–Meier method was used to estimate the cumulative incidence of recurrence, death and fertility, within each type of ovarian surgery, stratified for laterality of the disease or surgery [10]. Standard errors (s.e.) were calculated according to Greenwood's formula [11]. No competing risks were present for the recurrence analysis as all patients dying during follow-up recurred before death, nor for fertility analysis, as the two patients who died during follow-up also had a post-surgery conception. Potential confounder variables to be included in the models using Diacyclic graph (DAG) (DAGitty) [12] were selected on the basis of clinical expertise and previous studies. After verifying the proportional hazard assumption, a Cox model was used to investigate the association between time to first recurrence and the following variables: type of surgery, surgical approach, age, FIGO stage, histology and laterality of the tumour.

Similarly, a Cox model was used to investigate the association between time to first post-surgical pregnancy and the following variables: type of surgery, surgical approach, number of surgery (before first pregnancy or radical surgery), age, histology, laterality of the surgery, previous pregnancies and FIGO stage. Both models were stratified by decade of the intervention. The interaction between the type of surgery and surgical approach was tested and omitted from the final model if not significant. Results of the Cox models are presented for the oncologic outcome as hazard ratios (HRs) of recurring vs. not recurring after surgery and for the fertility outcome as HR of having at least a conception vs. not conceiving with 95% confidence intervals (CIs). All analyses were performed using R software (3.1.0; R Core Team 2014, Vienna).

3. Results

Among 898 patients treated for BOT between 1978 and 2013, 362 underwent bilateral SO and 1 patient was lost to follow-up. Therefore, 535 undergoing FST were included in the analysis: 271 (50.7%) patients underwent SO, whereas 264 (49.3%) Cy (Supplementary Fig. 1). SO was the most common procedure before 2000 as it was performed in 57% (154/270) of patients, whereas it was less frequent after 2000 (117/265, 44%). The clinical features were similar in the two treatment groups (Table 1). Median age at diagnosis was 29.8 years (I-III quartiles, 25.3–34.4 years), with 65.6% of patients ($N = 351$) with no prior pregnancies before diagnosis. Patients with FIGO stage I tumours were 81.9%, whereas 18.1% had advanced-stage disease. Less than 1% of patients ($N = 4$) had invasive implants, and 7.9% ($N = 42$) did not have invasive implants; 81.9% of patients did not undergo peritoneal biopsies, and 30 patients underwent nodal sampling. Surgical procedures on both ovaries were performed in 173 (32.3%) patients, with confirmed bilateral tumour diagnosis at final pathology in 16.4% of the population. Eleven percent ($N = 60$) of the population underwent adjuvant platinum-based chemotherapy because of advanced disease ($N = 29$) or for initial treatment outside our institution for unspecified reasons ($N = 31$). Overall, microinvasion and micropapillary patterns were present in 34 and 16 cases, respectively. These features were reported starting from early 2000s and therefore excluded from the analysis.

Median follow-up after diagnosis was 12.4 years (95% CI: 11.8–13.3). Overall, 25% of patients underwent a single surgery, 45.2% two, 15.9% three and 13.8% four or more surgical procedures. Sixty-six of 401 secondary surgical procedures (16.5%) were performed for recurrence, and 301 (75.1%) for surveillance (restaging or follow-up). Indications for every surgical procedure are displayed in Table 2.

3.1. Recurrence and death outcome

Characteristics of the recurrent population are described in supplementary Table 1. In the FST cohort, there were a total of 192 first recurrences, 87 in the SO (45.3%) and 105 (54.7%) in the Cy group. The overall 10-year (yr) cumulative probability of recurrence was 33.5% (95% CI: 29.5–38.0) overall, 27.4% (95% CI: 22.2–33.4%) for SO and 39.9% (95% CI: 33.9–46.6%) for Cy group. In the unilateral tumour group ($N = 447$), 10-yr recurrence rate was 22.9% (95% CI: 17.9–29.1%) for SO ($N = 241$) and 30.7% (95% CI: 24.5–38.0%) for Cy group ($N = 206$) (Log-rank test $P = 0.10$). In the bilateral tumour group ($N = 88$), 10-yr recurrence rate was 61.7% (95% CI: 44.1–79.4%) in SO ($N = 30$) and 72.0% (95% CI: 58.8–83.9%) in Cy group ($N = 58$) (Log-rank test $P = 0.35$) (Fig. 1, left).

Overall, excluding 33 patients with unknown data, the site of recurrence was ovarian only in 85.5% of cases, ovarian and extra-ovarian in 9.4% and extra-ovarian in 5.0%. For unilateral tumours in the Cy group, ovarian ipsilateral relapses occurred in 31 of 206 (15%) cases, bilateral in 10 of 206 and contralateral in 10 of 206 (4.9%) cases. In the SO group, relapses occurred in 21.6% of patients (52/241) in the remaining contralateral ovary.

Progression to invasive disease occurred in 8 cases: 4 patients at first relapse, 3 at second one patient at third. Four of them had undergone SO, and 4 Cy at the first surgery. Among these patients, 3 patients who presented with a diffuse relapsing disease were treated with radical surgery; all of them eventually died of disease. The remaining 5 patients were successfully treated with FST and underwent radical surgery after completion of childbearing desire, without experiencing any further relapse.

Table 1
Demographic and clinical characteristics of patients included in the analysis according to surgical treatment ($N = 535$).

Characteristic	*Total*	*Salpingo-oophorectomy (SO)*	*Cystectomy (Cy)*	*P-value*[a]
	N = 535	*N = 271*	*N = 264*	
Median(I, III quartiles)				
Age	29.8 (25.3, 34.4)	30.5 (25.9, 35.4)	29.2 (24.3, 32.8)	0.001
No. of patients (%)				
Previous pregnancies				0.90
Yes	184 (34.4)	92 (33.9)	92 (34.8)	
Pregnancy desire				0.29
Yes	252 (47.1)	121 (44.6)	131 (49.6)	
FIGO stage				<0.001
Stage IA	248 (46.4)	140 (51.7)	108 (40.9)	
Stage IB	29 (5.4)	12 (4.4)	17 (6.4)	
Stage IC	161 (30.1)	61 (22.5)	100 (37.9)	
Stage IIA-C	37 (6.9)	18 (6.6)	19 (7.2)	
Stage IIIA-C-IV	60 (11.2)	40 (14.8)	20 (7.6)	
Tumour laterality				0.001
Bilateral	88 (16.4)	30 (11.1)	58 (22.0)	
Surgical procedure				0.13
Bilateral	173 (32.3)	79 (29.2)	94 (35.6)	
Histotype				0.15
Serous	333 (62.2)	160 (59.0)	173 (65.5)	
Mucinous	202 (37.8)	111 (41.0)	91 (34.5)	
Implants				0.22
Negative	51 (9.5)	31 (11.4)	20 (7.6)	
Not invasive	42 (7.9)	24 (8.9)	18 (6.8)	
Invasive	4 (0.7)	3 (1.1)	1 (0.4)	
Not assessed	438 (81.9)	213 (78.6)	225 (85.2)	
Washing				0.45
Negative	193 (36.1)	91 (33.6)	102 (38.6)	
Positive	65 (12.1)	33 (12.2)	32 (12.1)	
Not performed	277 (51.8)	147 (54.2)	130 (49.2)	
Number of surgeries				0.30
1	134 (25.0)	67 (24.7)	67 (25.4)	
2	242 (45.2)	131 (48.3)	111 (42.0)	
3	85 (15.9)	44 (16.2)	41 (15.5)	
≥4	74 (13.8)	29 (10.7)	45 (17.0)	
First surgical approach				0.74
LPS	244 (45.6)	126 (46.5)	118 (44.7)	
Open	291 (54.4)	145 (53.5)	146 (55.3)	
Adjuvant treatment				0.09
Yes	60 (11.2)	37 (13.7)	23 (8.7)	

Abbreviations: FIGO= International Federation of Gynecology and Obstetrics; LPS, laparoscopy.
[a] Categorical variables were compared between groups using χ^2 test or Fisher test, as appropriate; age and the number of surgeries were compared using the Mann–Whitney U test.

Ten-yr cumulative incidence of death was 1.3% (95% CI: 0.4–3.9%) for SO and 2.9% (95% CI: 1.4–6.0%) for Cy group. No differences in the incidence of death were found at univariable analysis between the two groups, both in the unilateral ($P = 0.39$) and bilateral tumour group ($P = 0.70$) (data not shown).

Table 2
Distribution of subsequent surgeries after primary surgery.

Indication for subsequent surgery	Surgery number						Total	
	2nd	3rd	4th	5th	6th	7th		
Number of procedure	N = 401	N = 159	N = 74	N = 28	N = 6	N = 3	N	%
Recurrence	66	97	44	14	4	3	228	34.0
Surveillance (restaging or follow-up)	301	48	19	5	2	0	375	55.9
Radical surgery (not for recurrence)[a]	25	9	11	8	0	0	53	7.9
Other[b]	9	5	0	1	0	0	15	2.2
TOTAL	**401**	**159**	**74**	**28**	**6**	**3**	**671**	

[a] Radical surgery includes patients' choice to remove the genital tract after childbearing attempt.
[b] Other reasons include other benign ovarian diseases.

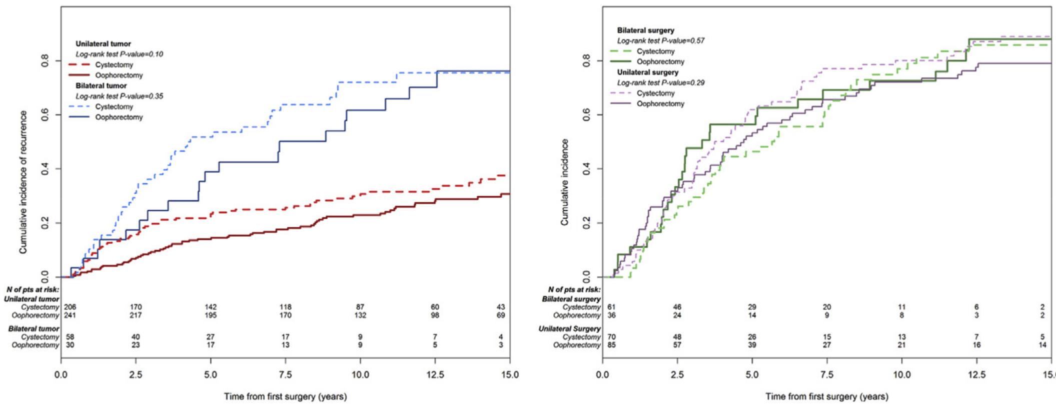

Fig. 1. Cumulative incidence of (left) first relapse after surgery in women with BOT undergoing conservative surgery, according to the type of ovarian surgery at diagnosis and laterality of the tumour ($N = 535$); (right) first pregnancy after surgery in the subgroup of women with desire of pregnancy, according to the type of ovarian surgery at diagnosis and laterality of the cysts ($N = 252$). BOT, borderline ovarian tumour.

Results of the multivariable Cox model investigating the association between surgical features and first recurrence in patients who underwent FST are presented in Table 3. Type of surgery (HR Cy vs. SO: 1.34, 95% CI: 0.98–1.81, $P = 0.06$) and surgical approach (HR open vs. LPS: 1.12, 95% CI: 0.84–1.5, $P = 0.44$) were not associated with increased risk of recurrence, whereas advanced stage (HR stage Ic-II vs. Ia-Ib: 1.46, 95% CI: 1.05–2.03, $P = 0.024$; HR stage III-IV vs. Ia-Ib: 3.18, 95% CI: 2.11–4.78, $P < 0.0001$) and bilateral tumour conferred higher risk of recurrence (2.48, 95% CI: 1.78–3.47, $P < 0.0001$). The risk of recurrence did not differ between tumour histology, even when the analysis was carried out by subtypes separately (Supplementary Table 2).

3.2. Fertility outcome

Among patients undergoing FST, 252 (47.1%) patients had pregnancy desire and 283 patients were excluded due to a diagnosis of primary infertility before surgery ($N = 11$), no desire of pregnancy ($N = 253$) or unknown pregnancy desire ($N = 19$). Characteristics of the patients with and without pregnancy desire were similar (supplementary Table 3). In the subgroup of patients with pregnancy desire, the cumulative incidence of recurrence did not differ between SO and Cy groups, both in patients with unilateral and bilateral tumours (supplementary Fig. 2). Multivariable analysis did not show increased risk associated with a specific surgical feature (HR Cy vs. SO 0.95, 95% CI: 0.63–1.43, $P = 0.81$) (data not shown).

The total number of women experiencing at least one pregnancy was 212, 101 (47.6%) in the SO and 111 (52.4%) in Cy group. The 15-yr overall cumulative incidence of first pregnancy in our population was 84.6%. Among women with unilateral cyst ($N = 155$), the cumulative incidence of first pregnancy at 15 years was 83.4% (95% CI: 76.8–89.0%), whereas in patients with bilateral cysts ($N = 97$), it was 86.7% (78.1–93.1%). Cumulative incidence of first pregnancy after surgery stratified in classes is shown in Fig. 1, right. In the group undergoing unilateral surgery, the 15-yr pregnancy incidence was 79.0% (69.4–87.2%) in SO and 88.9% (79.7–95.2%) in Cy group. In the bilateral cyst group, 15-yr pregnancy incidence was 88.0% (73.2–96.7%) in SO and 85.9% (74.7–93.8%) in Cy group.

Results of the multivariable Cox model investigating the association between surgical features and fertility are shown in Table 4. Type of surgery (HR Cy vs. SO: 1.15, 95% CI: 0.86–1.54, $P = 0.36$) and surgical approach (HR open vs. LPS: 0.87, 95% CI: 0.65–1.18, $P = 0.37$) were not associated with fertility. Previous pregnancies were associated with higher fertility (HR: 1.68, 95% CI: 1.17–2.41, $P = 0.005$). Instead, each additional surgical intervention after first surgery, either for recurrence or for surveillance, reduced the probability of pregnancy by about 40% (HR: 0.62, 95% CI: 0.53–0.73, $P < 0.0001$). No differences in the probability of pregnancy were found for tumour histology and tumour laterality.

At term pregnancy, proportions in the two groups were similar, being 80.2% ($N = 97$, 95% CI: 71.7–86.6%) in SO and 80.1% ($N = 105$, 95% CI: 72.1–86.4). There were 20 spontaneous abortions in SO and 29 in Cy group; 73 patients had two term pregnancies, and 11 had three or more term pregnancies (Supplementary Table 4).

4. Discussion

Our data confirm that young women with BOT can be safely treated with FST, even if the overall 10-year probability of recurrence in our series is 33.5% (95% CI: 29.5–38.0). This value is higher than the probability reported for radical treatment that varies from 12

Table 3
Results from the multivariable Cox model investigating the association between type of surgery and first recurrence in women with a borderline ovarian tumour undergoing conservative surgery ($N = 535$).

Variable	*N recurring/N*	*HR*	*(95% CI)*		*P-value*
Type of surgery					
Salpingo-oophorectomy (ref.)	87/271				
Cystectomy	105/264	1.34	0.98	1.81	0.06
Surgical approach					
Laparoscopy (ref.)	80/244				
Open surgery	112/291	1.12	0.84	1.5	0.44
Age (5-year increments)		0.91	0.81	1.02	0.12
Histotype					
Serous(ref.)	122/333				
Mucinous	70/202	0.98	0.73	1.32	0.91
Stage					
IA-IB (ref.)	72/277				
IC-II	76/198	1.46	1.05	2.03	0.024
III-IV	44/60	3.18	2.11	4.78	<0.0001
Laterality of the tumour					
Unilateral (ref.)	132/447				
Bilateral	60/88	2.48	1.78	3.47	<0.0001

Table 4
Results from the multivariable Cox model investigating the association between type of surgery and fertility in the subgroup of women with pregnancy desire ($N = 252$).

Variable	*N fertile/N*	*HR*	*(95% CI)*		*P-value*
Type of surgery					
Salpingo-oophorectomy (ref.)	101/121				
Cystectomy	111/131	1.15	0.86	1.54	0.36
Surgical approach					
Laparoscopy (ref.)	92/110				
Open surgery	120/142	0.87	0.65	1.18	0.37
Number of interventions (any additional intervention)		0.62	0.53	0.73	<0.0001
Age (5-year increments)		1.13	0.97	1.31	0.12
Histotype					
Serous (ref.)	129/154				
Mucinous	83/98	1.15	0.86	1.52	0.35
Stage					
IA-IB (ref.)	97/113				
IC-II	89/107	1.07	0.8	1.44	0.64
III-IV	26/32	1.37	0.86	2.18	0.19
Laterality of the intervention					
Bilateral (ref.)	79/97				
Unilateral	133/155	0.92	0.67	1.25	0.59
Previous pregnancy					
No (ref.)	154/187				
Yes	58/65	1.68	1.17	2.41	0.005

to 58% [13–16]. However, most of our recurrent cases were successfully treated, with only 1.5% of the patients dying of disease progression, as similarly reported in the literature (0–3%) [13,17–20] (Supplementary Table 5).

In our population, surgical approach did not influence recurrence or fertility. The main advantage of the mini-invasive approach is the reduced morbidity [21], including in particular the reduction of post-operative adhesions that could possibly impair fertility. On the other hand, laparoscopic experience by gynaecologic oncologists is crucial to avoid cyst fluid spillage and limitation of healthy ovarian tissue ablation, maximising the oncologic and reproductive outcomes. The choice of surgical approach should be based on the dimension of the suspicious mass, the presence of adhesions and surgical invasiveness, avoiding to treat large cysts by LPS, thus enhancing peritoneal tumour persistence and early relapse [22].

Even if the most effective type of surgery (SO vs. Cy) in BOT has been widely studied, no univocal data are available regarding the risk of recurrence: some authors observed an increased risk of relapse related with Cy [16,19], whereas others reported a similar risk compared to SO [14,18,23,24]. A recent meta-analysis [20] reported a higher risk in Cy group with a pooled recurrence rate of 25.3% and 12.5% (Cy vs. SO) and pooled odds ratio of: 2.174 (95% CI: 1.681–2.811, $P = 0.0001$).

In our experience, we observed a relapse rate of 30.7% and 22.9% for Cy and SO, respectively, that was similar to the meta-analysis data, whereas no statistically significant impact in the multivariable analysis was observed (Table 3). Even though it is conceivable that some relapse protection by SO can be obtained, additional considerations are important to be taken into account.

1) The more radical approach (SO) did not protect patients from contralateral relapses: 52 of 241 patients (21.6%) had a contralateral relapse in the SO group and 20 of 206 (9.7%) in the cystectomy group with unilateral tumours (χ^2 test, P: <0.001). Contralateral relapse can be deleterious for fertility, especially when the patient has already removed the other ovary, leaving lower amount of healthy ovarian tissue.
2) Three patients who underwent subsequent surgeries after primary treatment experienced ovarian failures. All these patients had bilateral tumours initially treated with SO (N = 1), Cy (N = 1) and bilateral Cy (N = 1) and experienced POF after less than 12 months after a second FST surgery for relapse.
3) A significant number of patients (N = 80) underwent bilateral ovarian surgery due to suspicious tumours, but BOT was confirmed only in one ovary. In these cases, a more careful preoperative assessment could have prevented an unnecessary (and potentially harmful) procedure.

Therefore, it emerges from our analysis that rather from the surgical procedure itself (SO vs. Cy), fertility is mainly impaired by the number of surgical interventions, as reported for other benign diseases [25]. Reducing the number of repeated gonadal surgeries should be the aim when planning FST for a woman with BOT because every spared surgery for the patient would prevent a reduction in fertility of about 40% (Table 4).

The results in terms of fertility in our population were satisfactory, higher than those of previous reports [20], possibly due to the long follow-up. Fertility after surgery was related to presurgical fertility; however, nulliparous women also had a high fertility rate with a 15-year first pregnancy probability of 82.5% (76.2–88.0) and a median age at first pregnancy of 32 years. The fraction of infertile population was low and comparable with that of the general population of Western countries [26], with common reasons for infertility such as male infertility ($N = 5$) and benign disease such as endometriosis or tubal obstruction ($N = 7$). Of note, 199 out of 212 successful pregnancy attempts were obtained by spontaneous conceptions, the others by in vitro fertilisation.

The limitation of the study is its retrospective nature that could cause selection biases. However, the population at study was retrieved consecutively, underwent centralised pathologic review and was closely monitored in a referral hospital, accounting for the biggest single-center data set to date (Supplementary Table 5).

In conclusion, our study showed that different surgical approaches performed by experienced gynaecologic oncologists lead to comparable oncologic and fertility outcomes. Cy might be the best procedure for young women, sparing a higher amount of ovarian tissue. The number of surgeries might be limited, tailoring the primary treatment and the subsequent follow-up to each individual patient, avoiding, when feasible, aggressive treatment of the relapse and identifying the best timing of the intervention in relation to the attempt of conception.

Finally, the follow-up should not be discontinued because in our series, in accordance to large multicenter reports [16], the relapse risk did not show any reduction even after 10-yr follow-up (Fig. 1): A genomic progression between BOT and low-grade ovarian cancer is known [27], and possible shifts towards invasive disease have to be taken into account.

Authors' contribution

Martina Delle Marchette, Lorenzo Ceppi, Anita Andreano and Robert Fruscio contributed to the conception and design of the study. Martina Delle Marchette and Lorenzo Ceppi contributed to collection and assembly of data. All authors contributed to data analysis and interpretation and manuscript writing, approved of the final version of the manuscript and are accountable for all aspects of the work.

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None.

Conflict of interest statement

All authors declare no conflict of interest.

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Appendix A. Supplementary data

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