Evaluation of Prognostic Factors for Survival in Women with Borderline Ovarian Tumors

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Abstract

Objective: To evaluate the clinico- pathological features and modalities of treatment that affect recurrence and survival in patients with borderline ovarian tumors.

Methods: Data of 92 patients diagnosed with borderline ovarian tumors (BOTs) during the period from 2005 to 2017 in the National Cancer Institute (NCI) and Menoufia University Hospital, Egypt, were retrospectively analyzed.

Results: Median follow-up period was 76 months (range, 12-157 months). Histopathology was serous in 63%, mucinous in 28.3%, and endometrioid in 3.3%. Sixty five patients (70.7%) had Stage IA disease, 17 patients had Stage IB disease (18.5%), and 10 patients had advanced disease. Forty nine patients (53.3%) underwent fertility sparing surgery and 43 patients (46.7%) underwent radical surgery. The total recurrence rate was 18.5% (17/92); three patients (17.6%) among those who underwent radical surgery and fourteen patients (82.4%) among those who received fertility sparing surgery. Twelve of the recurrences (70.6%) were borderline while 5 were invasive (29.4%). Multivariate analysis showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival. Risk factors for recurrence in the fertility sparing surgery group were stage, microinvasion and elevated preoperative serum CA125.

Conclusion: When considering conservative surgery in patients with borderline ovarian tumors, special care should be given to patients with elevated CA-125, advanced FIGO stage, and microinvasion.

Keywords: Borderline ovarian tumors, Prognostic factors, Survival.

Introduction

Borderline ovarian tumors were first described by Taylor in 1929 when he noted a group of "" ovarian tumors that were associated with a favorable prognosis [1].They were first recognized as a separate pathologic and clinical entity by the International Federation of Gynecology and Obstetrics (FIGO) in 1971 and was followed by World Health Organization acceptance in 1973 [2].

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They represent a specific group of epithelial ovarian neoplasms that are histologically distinguished from ovarian carcinomas by the absence of stromal invasion. These neoplasms are also referred to as tumors of low malignant potential (LMP), which reflects their indolent natural history [3].

BOTs comprise approximately 15 % of all epithelial ovarian tumors; the mean age of occurrence is approximately 10 years younger than that of women with frankly malignant ovarian cancer, a fact that emphasizes the importance of fertility-sparing surgery in patients who want to preserve their childbearing potential [4, 5].

Surgery is the main treatment modality for BOTs, but considerable debates exist on the extent of surgery. Some surgeons do not perform the complete staging because the survival is high regardless of stage [5]. Borderline Ovarian Tumors are associated with a significantly more favorable prognosis than epithelial ovarian cancer, the 5-year overall survival rate for early stage I BOT is approximately 98%; and the 5-year overall survival of advanced disease is between 86% and 92% [6].Follow up should be long term because recurrences may develop after more than 15 years. In conservatively treated women, close follow up is crucial, with special attention to the remaining ovary [7].

In the current study, we evaluated the clinico- pathological features and modalities of treatment that may affect the recurrence rate and survival in such patients.

Patients Methods

The present study was approved by the local ethical committee of the National Cancer Institute (NCI) and Menoufia University Hospital, Egypt, where the study was conducted. The files of 92 patients who were diagnosed and treated for borderline ovarian tumor were retrospectively reviewed between March 2005 and February 2017. From the hospital records, data related to the patients' age, menopausal state, parity and pre-operative CA-125 (Cancer Antigen-125) were collected. Furthermore, type of surgical technique, histopathologic type, mean tumor diameter, presence and characteristics of tumor implants, results of the peritoneal washings, lymph node status, stage at the diagnosis, and accompanying pathologies if any, were reviewed. Additionally, chemotherapy requirements after surgery, postoperative follow-up periods, and data related with the disease recurrence and conditions necessitating recurrent operations were evaluated.

Pathological staging was done according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) 2014. Comprehensive surgical staging with peritoneal sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, appendectomy and omentectomy were performed in patients who were postmenopausal, completed their family or had additional disease that required extensive surgery. Fertility sparing surgery retaining the uterus and the adnexa at one or both sides were performed in patients who were premenopausal and wish to preserve their fertility. Types of fertility preserving surgery performed were: unilateral salpingo-oophorectomy (USO), unilateral salpingo-oophorectomy plus contralateral ovarian cystectomy, unilateral ovarian cystectomy and bilateral ovarian cystectomy. All patients were operated on using open surgery.

Chemotherapy was recommended for all BOT patients with lymph node metastasis, or invasive implants, or with stage III/IV. Follow- up of patients was performed once every 3 months in the first 2 years and every 6 months in the next 3 years and yearly thereafter. At the time of follow-up, patients received routine gynecological examination, test for tumor markers and ultrasound.

If tumor markers and/or ultrasound were abnormal, then patients would be examined by CT. Recurrence was defined as the same tumor cell type detected after an apparent complete surgical resection. Disease free survival (DFS) was defined as the time from the date of surgery to the date of recurrence or to the last date of follow-up. Patients with incomplete data were excluded.

Statistical analysis: The collected data, were tabulated and analyzed by IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range. Qualitative data were expressed as frequency and percentage. Univariate analysis was done to assess association between individual variables with disease free survival and recurrence. The survival curves and rates were calculated using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. A p-value < 0.05 was considered significant.

Results

A total of 92 BOT cases were identified. Patients and disease-related characteristics are shown in Table I. The mean age at primary diagnosis was 42.7 years (range=15-71 years); 66.3% (n=61) of women were premenopausal and 33.7% (n=31) were postmenopausal. Serum CA125 was elevated in 47 patients (51.1%). The tumor was larger than 11 cm in 49 patients (53.3%) and malignant ascites was present in 7 patients (7.6%).

Histopathology revealed serous BOT in 61 (66.3%) patients which was considered the most frequent pathologic type, 23 patients had mucinous BOT (25%), endometrioid in 3 patients (3.3%), mixed in 4 patients (4.3%), and only one patient had Brenner tumor (1.1%).

In sixty five patients the disease was stage IA (70.7%) and the remaining 27 patients were: stage 1 B (18.5%, n=17), stage 1C (4.3%, n=4), stage II (2.2%, n= 2), stage III (4.3%, n=4). Forty patients had micropapillary disease (43.5%) and two patients had microinvasion (2.2%). Implants were found in 6 (6.5%) patients of whom 1 patient had invasive implants. They were localized at the omentum, tubes, peritoneum, parametria, Douglas pouch, uterus, cervix, lymph nodes, sigmoid, rectum and appendix.

Details of the surgical procedures and adjuvant chemotherapy are given in Table 2. Forty nine patients (53.3%) underwent fertility sparing surgery, of whom 19 patients underwent unilateral ovarian cystectomy, 5 patients underwent bilateral ovarian cystectomy, 25 underwent unilateral salpingo-oopherectomy.43 patients (46.7%) underwent radical surgery including total abdominal hysterectomy and bilateral salpingo-oophorectomy. Eighty three patients (90.2%) had their primary surgery without grossly detected residual disease or cyst rupture. Tumor rupture occurred during surgery in 5 patients (5.4%). Pelvic and para-aortic lymph nodes were sampled in ten patients, none of which showed tumor invasion. Postoperative adjuvant chemotherapy was given in two patients who had peritoneal implants using regimen of paclitaxel and carboplatin 3-6 cycles.

Table 1: The main patient and disease characteristics

Studied variables	No.	%
Age / years		
- ≤40	51	55.4
- >40	41	44.6
Mean ±SD	42.7±15.8	
Range	15 – 71	
Parity		
- Nullipara	22	23.9
- Multipara	70	76.1
Menopausal status		
- Premenopausal	61	66.3
- Postmenopausal	31	33.7
Ultrasound finding		
- Solid	53	57.9
- Cystic	20	21.7
- Multi-loculated	19	20.7
Ascites		
- Positive	7	7.60
- Negative	7	7.60
- Not available	78	84.8
CA 125		
- ≤ 35	45	48.9
- >35	47	51.1
Mean ±SD	134.1±236.4	
Median	44.5	
Range	4.70 – 1589	
Site		
- Right	40	43.5
- Left	32	34.8
- Bilateral	20	21.7
Size		
- ≤ 11	43	46.7
- > 11	49	53.3
Mean ±SD	13.5±6.17	
Range	4 – 30	
Histological subtypes		
- Serous	58	63.0
- Mucinous	23	28.3
- Endometrioid	3	3.30
- Brenner	1	1.10
- Mixed	4	4.30
Micropapillary		
- Yes	40	43.5
- No	22	23.9
- Not applicable	30	32.6

Microinvasion - Yes - No	 2 90	 2.20 97.8
Implants - Yes - No	 6 86	 6.5 93.5
Type of implant - Invasive - Non invasive	 1 5	 16.7 83.8

Table 2: Details of the surgical procedures and adjuvant chemotherapy

Studied variables	Studied group	
	No.	**%**
Type of surgery: **Fertility sparing** - Unilateral ovarian cystectomy - Bilateral ovarian cystectomy - Unilateral salpingo-oophorectomy **Radical surgery**	 **49** 19 5 25 **43**	 **53.3%** 38.8% 10.2% 51.0% **76.7%**
Lymphadenectomy - Yes - No	 10 82	 10.9% 89.1%
Residuals, cyst rupture - Yes - No - Unknown	 5 83 4	 5.40% 90.2% 4.30%
Adjuvant chemotherapy Yes No	 2 90	 2.2% 97.8%

Follow up and outcome

Details of the recurrence and survival are given in Table 3.The median follow-up period for the whole group was 76 months (range, 12-157 months). Recurrence of the disease was observed in 17 patients (18.5%) during follow up period, while 75 patients (81.5%) were disease free at the last follow up. The Mean time to recurrence (disease free survival) among patients was 104.4 months. Out of 17 patients who were recurred, 6 cases recurred in the same ovary, 7 cases recurred in the opposite ovary, one case recurred in both ovaries and 3 cases recurred in the peritoneum or LNs. Twelve of the recurrences (70.6%) were borderline whereas 5 were invasive (29.4%).Thirteen patients (76.5%) underwent surgery for recurrence, 1 (5.9%) received systemic chemotherapy, 2 (11.7%) treated by both surgery and chemotherapy and 1 (5.9%) received Hyperthermic Intraperitoneal Chemotherapy (HIPEC) plus surgery. Follow-up of those 17 patients revealed that they were all alive at the last contact. By the end of the study only one case died; she had stage III disease.

Table 3: Details of Recurrence and survival among patients treated for Borderline Ovarian Tumors:

Studied variables	Studied group	
	No.	%
Recurrence		
- Yes	17	18.5
- No	75	81.5
Site of relapse	N=17	
- Ipsilateral ovary	6	35.3
- Contralateral ovary	7	41.2
- Both ovaries	1	5.9
- Peritoneal or nodal	3	17.6
Type of relapse	N=17	
Borderline	12	70.6
Invasive	5	29.4
Treatment of relapse	N=17	
- Surgery	13	76.5
- Systemic Chemotherapy	1	5.90
- Surgery and chemotherapy	2	11.7
- HIPEC	1	5.90
Survival		
Died	1	1.10
Survived	91	98.9

Factors affecting recurrence and disease free survival

With Kaplan-Meier analysis, the mean disease free survival (DFS) was significantly higher in patients older than 40 years (75.6 months) (range, 69.8 – 81.5) than younger patients (69.7 months) (range, 59.7 – 79.5). Stages IA and IB had significantly higher disease free survival than other stages 79.7months (range, 73.2 – 86.1) versus 55.0 months (range, 29.6 – 80.4). Patients with microinvasion had significantly shorter disease free survival 10.5 months (range, 9.52 – 11.5) versus 77.6 months (Table 4).

Table 4: Disease free survival of BOTs and its relation to different prognostic factors

Prognostic factors		Disease free survival	SE	Log rank	P value
		Mean (95% CI)			
Age / years	≤ 40 > 40	69.7 (59.7 – 79.5) 75.6 (69.8 – 81.5)	5.04 2.97	4.68	**0.031***
Menopause	Pre Post	97.8 (80.0 -115.6) 76.2 (69.7 – 82.6)	9.10 3.31	3.00	0.083
Parity	Nullipara Multipara	63.2 (46.7 – 79.8) 80.0 (73.2 – 86.9)	8.46 3.50	3.27	0.070
Laterality	Unilateral Bilateral	76.5 (65.4– 87.7) 65.9 (57.8– 73.9)	5.68 4.09	0.770	0.680

Tumor size	≤ 11 > 11	71.7 (61.3 – 82.1) 73.0 (66.3– 79.7)	5.31 3.40	2.36	0.124
CA125	≤ 35 >35	82.6 (74.9 – 90.4) 68.7 (59.3 – 78.2)	3.94 4.83	2.73	0.098
Stage	IA&IB Other stages	79.7(73.2 – 86.1) 55.0 (29.6 – 80.4)	3.29 12.9	6.47	**0.011***
Histology	Serous Mucinous Others	74.0(65.5 – 82.5) 72.6 (62.7 – 82.5) 67.1(52.7 – 81.5)	4.34 5.03 7.36	0.794	0.672
Lymphadenectomy	Yes No	70.1 (46.2 – 94.1) 77.6 (70.8 – 84.5)	12.2 3.48	0.743	0.389
Microinvasion	Yes No	10.5 (9.52 – 11.5) 77.6 (70.9 – 84.1)	0.50 3.35	30.1	**0.001***
Micropapillary	Yes No Not applicable	73.2(62.3 – 83.4) 79.4 (67.9 – 90.8) 71.7(62.4 – 81.8)	5.22 5.85 4.74	0.618	0.734
Surgical ttt	Fertility sparing Radical	68.5(58.2 – 78.8) 75.8 (70.2 – 81.4)	5.26 2.86	5.65	**0.017***
Adjuvant chemotherapy	Yes No	11.0 (9.61 – 12.4) 76.1 (70.1 – 83.4)	0.70 3.41	5.22	**0.022***

***Significant**

Radical surgery had significantly higher DFS than fertility sparing surgery [75.8 months (range, 70.2 – 81.4)] versus 68.5 months (range, 58.2 – 78.8). Patients who received adjuvant chemotherapy had shorter DFS [11.0 months (range, 9.61 – 12.4)] versus 76.1 months (range, 70. 1 – 83.4).

Multivariate analysis showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival (Table 5).

Table 5: Multivariate Cox regression analysis for detection of the independent risk factors for worse disease free survival among BOTs patients:

Variable	WALD	Hazard ratio	P value
Age	1.02	0.792	0.311
Stage	3.47	1.27	0.062
Surgical ttt	6.57	3.13	**0.010***
Adjuvant chemotherapy	3.66	2.05	0.056
Micro invasion	0.135	0.607	0.714

***significant**

Univariate analysis of prognostic factors for disease free survival among fertility sparing surgery group suggested that FIGO stage, presence of microinvasion and elevated preoperative serum CA125 more than 35 IU/ml were significant risk factors for worse DFS (Table 6). The

mean disease free survival in patients treated with fertility sparing surgery was significantly higher in patients with preoperative serum CA125 less than 35IU/ml than those with preoperative serum CA125 more than 35 IU/ml; (80.1 months, range, 69.3 – 90.9) versus 53.1 months (range, 36.6 – 69.4) . Stages IA and IB had significantly longer disease free survival than other stages (73.1 months, range,62.8 – 83.4) versus 36.7 months(range,3.55 – 69.9). Patients with microinvasion had significantly shorter disease free survival 10.5 months (range, 9.52 – 11.5) versus 69.7 months (range, 59.5 – 80.0).

Table (6): Factors affecting disease free survival among fertility sparing surgery group (univariate analysis)

Fertility sparing group		Disease-free survival	SE	Log rank	P value
		Mean (95%CI)			
Age	≤ 45 years > 45 years	67.7 (56.6 – 78.7) 60.8 (39.4 – 82.2)	5.62 10.9	0.124	0.725
Parity	Nullipara Multipara	58.4 (39.1 – 77.8) 73.1 (60.9 – 85.3)	9.87 6.23	1.43	0.231
Laterality	Unilateral Bilateral ≤	70.1 (53.9 – 86.4) 57.6 (37.6 – 77.5)	8.29 10.1	0.492	0.782
Tumor size	≤11 cm > 11 cm	67.7 (61.3 – 81.2) 63.5 (49.8 – 77.2)	6.87 6.98	0.322	0.570
CA-125	≤ 35 IU /ml > 35 IU / ml	80.1 (69.3 – 90.9) 53.1 (36.6 – 69.4)	5.49 8.32	5.81	0.016*
FIGO stage	IA & IB Other stages	73.1 (62.8 – 83.4) 36.7 (3.55 – 69.9)	5.25 16.9	6.89	0.009*
Histopathologic subtypes	Serous Mucinous Others	64.2 (50.8 – 77.5) 72.0 (59.3 – 84.6) 51.0 (28.9 – 73.1)	6.82 6.45 11.2	1.57	0.456
Lymphadenectomy	Yes No	64.3 (15.2 – 113.3) 69.6 (58.8 – 80.4)	25.0 5.15	0.603	0.438
Microinvasion	Yes No	10.0 (10 – 10) 69.7 (59.5 – 80.0)	0.00 5.23	14.6	0.001*
Micropapillary	Yes No Not applicable	57.8 (40.2 – 75.3) 77.2 (60.9 – 93.6) 69.1 (56.1 – 82.1)	8.34 9.34 6.63	2.49	0.287
Type of fertility sparing surgery	-unilateral ovarian cystectomy -Bilateral ovarian cystectomy - Unilateral salpingo-oophorectomy	66.7 (50.1 – 83.4) 57.6 (37.6 – 77.5) 65.5 (51.1 – 80.2)	8.50 10.1 7.43	1.96	0.907

*Significant

However, multivariate analysis showed that microinvasion is the only independent risk factor affecting DFS among fertility sparing surgery group (table 7). In addition, there was no statistically significant difference regarding the overall survival in relation to type of surgery (table 8).

Table (7): Multivariate Cox regression analysis for detection of the independent risk factors affecting DFS among fertility sparing surgery group.

Variable	WALD	Hazard ratio	P value
FIGO stage	1.85	0.915	0.173
CA 125	0.648	0.612	0.421
Microinvasion	4.96	2.82	0.026 *

Table (8): The overall survival in relation to type of surgery

Fertility sparing group		Disease-free survival Mean (95%CI)	SE	Log rank	P value
Type of surgery	Fertility sparing Radical	90.5 (87.8 – 93.2) 79.3 (76.0 – 82.5)	1.38 1.65	0.07	0.788

Discussion

Borderline ovarian tumors are known to have usually an indolent nature with uncertain behaviors. Due to their atypical properties they are classified as a separate entity in the subject of ovarian malignancies. However, there are some features of BOTs that need special consideration such as peritoneal implants invasive or non-invasive, micropapillary architecture in serous BOT or presence of micro-invasion [8]. Furthermore, there are still debates related to type of surgical management, staging and adjuvant therapy.

This study has retrospectively analyzed the oncological outcomes of 92 borderline ovarian tumor patients with different clinico-pathological factors and different types of surgeries. It is expected that this study can help young patients with borderline ovarian tumor to select an optimal treatment. Borderline ovarian tumors are common in young women of childbearing age in which fertility-sparing surgery has been preferred. While the oncologic outcomes of BOTs patients after fertility-sparing surgery become a heated topic of discussion, there is no international guideline on this issue to help clinicians select treatment and follow-up plans. The results of the present study contain two important messages. The first one concerns the oncological result of BOTs. The second important point concerns the risk factors for recurrence after fertility-sparing surgery.

Regarding our data in terms of survival and relapse in relation to FIGO stage, we found that stages IA and IB had significantly higher disease free survival than other stages [79.7 months (73.2 – 86.1)] versus 55.0 months (29.6 – 80.4) which is in line with results of Du Bois et al and Trillsch et al who found that FIGO stage and sub-classification of extra-ovarian disease into invasive and noninvasive implants appear to be the major predictor not only for recurrence but also for survival [9,26]. Seong et al stated that the 5-year survival for stage I borderline ovarian tumor patients was approximately 95% to 97%, while the 5-year survival for stage II-III patients was only 65% to 87% [10].

In our study, microinvasion was found in 2.2% of patients and there was significant association between microinvasion and recurrence. Also, patients with microinvasion had significantly lower disease free survival [10.5 months (9.52 – 11.5)] versus 77.6 months (70.9 – 84.1). Consistent with these findings, Buttin et al found that recurrence rates were significantly higher in women with microinvasion compared to the rate of recurrence in women without microinvasion (23% versus 3.5%) [11].This is against Hogg et al who reported that microinvasion does not increase the chances of recurrence or affect the survival [12]. This difference may be due to the relatively small number of patients

with microinvasion in our study which is recognized as a considerable limitation to apply the finding of our series regarding the negative impact of microinvasion on the prognosis of borderline ovarian tumor.

Our results showed no difference in the disease free survival between different histopathologic subtypes which is similar to the findings of Loizzi et al [13]. On the contrary, Karlsen et al found a negative correlation between the serous histology and the risk of tumor relapse [14]. Chen et al demonstrated a longer recurrence interval in patients with serous borderline ovarian tumors who underwent fertility sparing surgery than those with mucinous tumors (35.9 versus 18.5 months, $P < 0.001$) [15]. Others observed that mucinous subtype-mostly in association with invasive implants has been associated with a worse prognosis in comparison to serous BOTs [16].

Unfortunately, the impact of micropapillary pattern on serous borderline ovarian tumor patients remains a source of controversy at present. Micropapillary architecture that was seen in 42% of our patients, was not a significant risk factor for recurrence or worse disease free survival in our study. Matching with these results, Du Bois et al found that the micropapillary growth pattern was not evidently associated with poor prognosis of borderline ovarian tumor patients [17]. Although many authors described it as risk factor for relapse or death from the disease, Chen Xi et al analyzed 178 borderline ovarian tumors patients and showed that micropapillary pattern was significantly associated with better DFS (P=0.0008) [18]. Conversely, Smith et al and Shih et al have shown that micropapillary histology is more associated with advanced stages, invasive implants, higher recurrence rates and lower survival [19, 20]. In comparing the typical borderline pattern with the micropapillary pattern in seven published studies, Lu and Bell found that both the relapse rate and death due to tumor were significantly increased in the micropapillary type (32% versus 15% and 15% versus 8%, respectively). Since these micropapillary types more often have invasive implants, it is difficult to discern the isolated impact of the micropapillary feature on survival [21].

In the current study, peritoneal implants were seen in 6.5% of the study population, and this was not significantly associated with recurrence or worse disease free survival. Several other studies have shown that borderline ovarian tumors with invasive implants are associated with an increased risk of recurrence and often a more aggressive clinical course [22]. In a review published in 2002 by Seidman and Kurman involving 245 studies and 4,129 patients, the survival rate for patients with invasive implants was 66% after a mean follow-up period of 7.4 years, compared to 95% for patients with noninvasive implants [23].

Our study showed that the recurrence rate in patients underwent fertility sparing surgery was notably higher than that of patients received radical surgery (28.6% versus 7%, $P = 0.008$*). Trillsch et al. reported a recurrence rate of 10-20% in patients underwent fertility sparing surgery, which was markedly higher than that in those received radical surgeries (5%) [9].Multivariate analysis of our cases showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival among patients of borderline ovarian tumor. Duration of disease-free survival were significantly shorter in cases managed by fertility sparing surgery than radical surgery [68.5 months (58.2 – 78.8)] versus 75.8 months (70.2 – 81.4). However, other studies reported that fertility sparing surgery is not regarded as a prognostic factor for recurrence [13].

In our series, a univariate analysis was performed to identify risk factors for worse disease free survival and subsequent recurrence in patients who underwent fertility sparing surgery (no=49). FIGO stage, elevated CA 125 > 35 IU/ml and presence of

microinvasion were significant risk factors. However, multivariate analysis confirmed only microinvasion as an independent risk factor for recurrent disease. Conversely, in the large series of Morice et al (2012), the risk of recurrence after conservative surgery was not related to microinvasion [8].

Fertility-preserving surgery can be performed in different types with different impacts on oncologic and pregnancy outcomes of BOT patients. In comparison to salpingo-oophorectomy, cystectomy retains more normal ovarian tissue and increases pregnancy success rate. On the other hand, cystectomy carries a significantly higher risk of recurrence [9]. In terms of different forms of fertility sparing surgery, our results showed that disease-free survival did not differ significantly between unilateral ovarian cystectomy compared to salpingo-oophorectomy (66.7months (50.1 – 83.4) versus 65.5 months (51.1 – 80.2).

Whether conservative surgery is appropriate for borderline ovarian tumors is an important matter to be resolved. In our study, the recurrence rate after conservative surgery was high (28.6%, nearly one-third of patients), but fortunately the great majority of the recurrent tumors were borderline lesions with no impact on outcome nor survival and only two patients had invasive recurrence. Moreover, the two patients were successfully treated with second round radical surgery and were alive and disease free by the end of the study. Likewise, a recent review of literature concerning the risk of recurrent invasive BOT among1500-1800 conservative surgical procedures, only 10 cases were reported [8]. Similarly, Zanetta et al reported a recurrence rate of 17% (28/164) in 164 patients treated with fertility sparing surgery for stage I borderline ovarian tumor, with 23 patients had borderline recurrence and 5 patients had invasive disease. Our results, therefore, do not challenge the use of conservative surgery as the standard of care in young patients with BOTs. Nevertheless, they indicate that the risk of an invasive recurrence exists and, hence, the risk of death. A careful and prolonged follow-up is, therefore, mandatory and patients should be informed of this rare risk.

Concomitantly, the overall survival in our study was statistically non-significant when compared between patients who underwent fertility sparing surgery and those who received radical surgery. The only one patient who died had FIGO stage III with invasive implants. Analogous to these findings, Donnez et al reported that although recurrence was more common in cases treated by conservative surgery (3 out of 16, 18.7%) than by radical surgery (0 out of 59, 0%), subsequent treatment resulted in no tumor-related deaths [25].

The present study is retrospective with a relatively small number of patients that represents a major limitation to apply the findings reported here. Additionally, the reproductive outcomes of BOT patients after fertility sparing surgery were not available. Moreover, Only 2 borderline ovarian tumor cases had microinvasion which is recognized as another considerable limitation. Consequently, studies including a large cohort size and a long-term follow-up period are needed to evaluate the correlation between microinvasion and prognosis of borderline ovarian tumors after fertility sparing surgery.

Conclusion

In conclusion, although recurrence was detected in 17 out of 92 cases with borderline ovarian tumor, no tumor-related deaths were found, and patients had a favorable long-term prognosis. Recurrences are amenable to treatment with completion surgery.

Fertility-sparing surgery is an acceptable and appropriate option for patients with BOTs who wish to preserve fertility. The higher risk of local relapse is not associated with decreased overall survival. When

considering conservative surgery in patients with borderline ovarian tumor, special care should be given to elevated CA-125, advanced FIGO stage or microinvasion. To reinforce the present study results, we expect that a large scaled prospective clinical study involving many institutions will be performed to obtain more evidence.

Author contributions

NIE, MEE, and MZS contributed to study design. NIE, MZS, ASH, NMH, and AA performed data collection; all authors contributed to analyses, interpretation of data, manuscript preparation and revising it critically.

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Conflict of interest

None

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