Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(2): 051
http://doi.org/10.31083/j.ceog4902051

Original Research

Is ovarian cystectomy feasible for patients with borderline ovarian tumors? A retrospective study and review of the literature

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Academic Editors: Alessandro Conforti and Michael H. Dahan
Submitted: 18 May 2021 Revised: 29 July 2021 Accepted: 20 August 2021 Published: 14 February 2022

Abstract

Background: Given that borderline ovarian tumors (BOTs) are usually found in young, fertile women without a history of childbirth, fertility preservation should be considered in the treatment plan. This retrospective study aimed to evaluate the safety of ovarian cystectomy in patients with BOTs. **Methods**: Patients with BOTs treated between August 2007 and August 2016 at our institution were divided into two groups according to the type of surgery: the cystectomy group and the oophorectomy group with or without salpingectomy, and differences in surgical outcomes were compared. The cumulative disease recurrence was also compared using Kaplan–Meier curves. **Results**: Of the 162 patients enrolled, 128 (79.0%) underwent an oophorectomy with or without salpingectomy and 34 (21.0%) underwent an ovarian cystectomy. The patients in the cystectomy group were younger than those in the oophorectomy group (29.2 years vs. 46.5 years, $p < 0.001$), and the proportion of patients who underwent minimally invasive surgery was higher in the cystectomy group than in the oophorectomy group (88.2% vs. 46.9%, $p < 0.001$). During the mean follow-up period of 44 months, six patients (3.70%) developed disease recurrence (five [3.9%] and one [2.9%] in the oophorectomy and cystectomy groups, respectively). The two-year disease-free survival rate was 97.1% and 97.6% in the cystectomy and oophorectomy groups, respectively, and did not differ between the groups ($p = 0.818$). **Discussion**: Ovarian cystectomy can be considered a safe and effective option for young women with BOTs who wish to preserve their fertility.

Keywords: Borderline ovarian tumor; Fertility sparing; Ovarian cystectomy; Oophorectomy

1. Introduction

Ovarian tumors with low malignant potential are a type of epithelial ovarian neoplasm, which has features between those of ovarian cancers and benign neoplasms [1]. These are also known as borderline ovarian tumors (BOTs) and were first described in 1929. The histologic diagnosis of BOTs requires an absence of stromal invasion and two of the following four features: complex arborizing papillary configuration, mitotic figures with or without cytologic atypia, cell stratification with often greater than three cells, and micropapillary epithelial stratification [2].

The incidence of BOTs is reported to be 1.8–4.8 patients per 100,000 women per year, and the prognosis is favorable in most cases, even in advanced stages [3]. Compared to ovarian cancer, BOTs are diagnosed at an earlier stage and in patients of younger age, and BOT cases are characterized by longer survival and later recurrence than those of cases of invasive ovarian cancer [4]. The most important prognostic factors are the histologic features and extent of the disease at diagnosis [5].

The definitive treatment for BOTs is surgery, which may include bilateral salpingo-oophorectomy, total hysterectomy, or staged procedures [6]. Given that BOTs usually occur in young, fertile women with no history of childbirth, fertility preservation should be considered in the treatment plan [7]. However, the safety and associated outcomes of fertility-sparing surgeries have not yet been established.

Minimally invasive surgery (MIS) is one of the newest and most exciting developments in the field of gynecology, and in oncologic surgeries, the techniques are highly developed [8]. Fertility-sparing surgery via the laparoscopic approach had been performed in patients with BOTs [9]. The safety of laparoscopic fertility-sparing surgery for BOTs has been recognized, but its correlation with prognosis is still under investigation.

The purpose of this study was to evaluate the safety of ovarian cystectomy for BOTs by comparing its associated surgical and disease outcomes with those of oophorectomy, which were performed by MIS or laparotomy approaches.

2. Materials and methods

2.1 Study design

Patient data from our institution were collected including medical records, pathology reports, and surgical reports. Female patients who underwent ovarian cystectomy or oophorectomy with histologically confirmed bor-

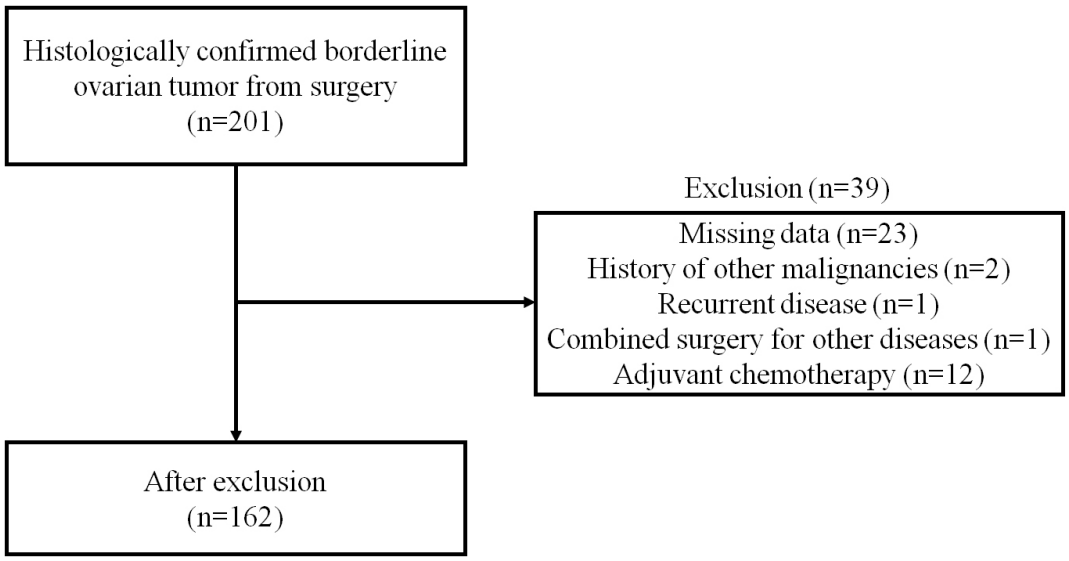

Fig. 1. Flowchart of study population selection.

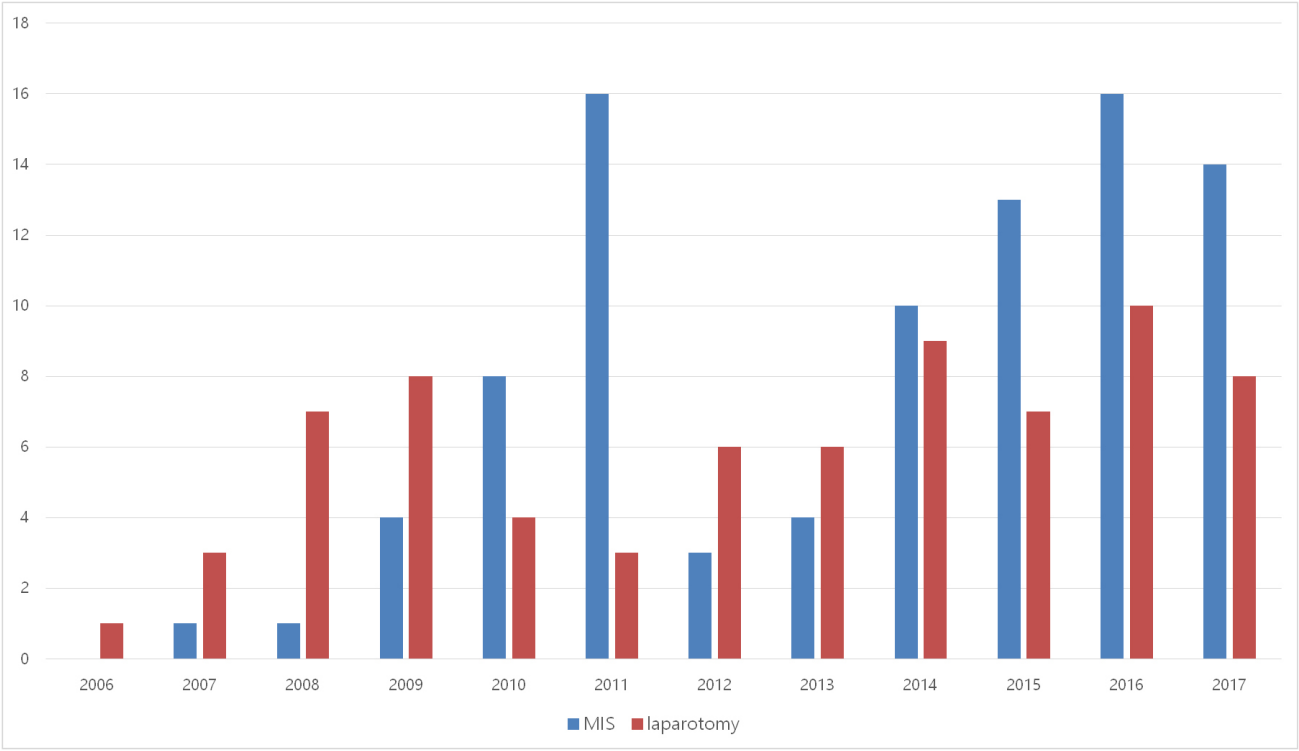

Fig. 2. Trend in the surgical approach for borderline ovarian tumor in our institution during the study period. MIS, minimally invasive surgery.

derline ovarian malignancies between 2007 and 2016 were included in this study. Patients with insufficient pathology or surgical data, those with combined ovarian epithelial malignancy, or who had adjuvant chemotherpay were excluded. The process of data collection and analysis was approved by the ethical review board of our institution (No. 2018AN0319).

2.2 Surgical procedures

The surgical approaches included laparotomy and MIS. For laparotomy, either a transverse or longitudinal incision was made according to the size of the ovarian tumor. MIS included both conventional laparoscopy and robotic-assisted laparoscopy. Three to five skin punctures were made based on the type of approach and the difficulty of the surgery.

Table 1. Clinical characteristics and disease outcomes for the study population.

	Cystectomy (n = 34)	Oophorectomy (n = 128)	*p*-value
Age (years), mean (SD)	29.2 (9.0)	46.5 (16.9)	<0.001
Parity, mean (SD)	0.50 (0.83)	1.51 (1.13)	<0.001
BMI (kg/m^2), mean (SD)	22.6 (3.9)	23.8 (3.7)	0.119
MIS, n (%)	30 (88.2%)	60 (46.9%)	<0.001
CA-125 before surgery, mean	343.1	609.9	0.781
Hb before surgery, mean	12.6	12.5	0.642
Hb after surgery, mean	10.7	11.1	0.088
Length of hospital stay, mean	5.47	8.75	0.001
Pre-operative impression, n (%)			<0.001
Benign	23 (67.6%)	17 (13.3%)	
Borderline tumor	11 (17.6%)	75 (58.6%)	
Malignant tumor	0 (0%)	36 (28.1%)	
Histopathology, n (%)			0.306
Serous	11 (32.4%)	29 (22.7%)	
Mucinous	19 (55.9%)	90 (70.3%)	
Seromucinous	3 (8.8%)	6 (4.7%)	
Other	1 (2.9%)	3 (2.3%)	
Stage, n (%)			0.685
I	34 (100%)	124 (96.9%)	
II	0 (0%)	1 (0.8%)	
III	0 (0%)	3 (2.3%)	
Tumor size (cm), mean (SD)	8.7 (6.1)	14.5 (7.5)	<0.001
Intraepithelial carcinoma, n (%)	2 (5.9%)	10 (7.8%)	0.746
Unintended tumor rupture, n (%)	7 (20.6%)	1 (0.8%)	<0.001
Recurrence, n (%)	1 (2.9%)	5 (3.9%)	0.791

BMI, body mass index; MIS, minimally invasive surgery; CA-125, cancer antigen 125; SD, standard deviation; Hb, hemoglobin.

Table 2. Risk of tumor rupture with cystectomy conducted using MIS.

	Cystectomy (n = 30)	Oophorectomy (n = 60)	*p*-value
Ruptured capsule	6	1	0.005
Intact capsule	24	59	

An ovarian cystectomy was defined as a surgery in which only cystic tumor lesions were removed and all intact ovarian tissue and the uterus were spared. The tumors were removed by cystectomy and the contralateral ovary was preserved when the patient's BOT was unilateral. For bilateral BOTs, a cystectomy was performed on both ovaries, and normal ovarian tissue was preserved. For the patients who underwent an oophorectomy or salpingo-oophorectomy, the affected ovaries were completely removed based on the extent of the disease. These cases included unilateral and bilateral tumors.

2.3 Post-operation

The histopathology reports included the histologic type and features of intraepithelial carcinoma. These reports were prepared by experienced and authorized pathologists from our institution's Department of Pathology. The serum levels of cancer antigen 125 (CA-125) was used to evaluate the pre-surgical trends of serum tumor markers.

Follow-up included a combination of clinical examinations, ultrasonography, computed tomography (CT), and assessment of tumor marker levels. In the first year after surgery, follow-up was scheduled for every three months, which includes ultrasonography or CT scan alternatively. Patients were then evaluated biannually for two years and annually thereafter, including annual CT scan till post-operative fifth year.

2.4 Statistical analysis

Descriptive statistics were used to determine the means and standard deviations for continuous variables. Mann-Whitney U tests and Students' *t*-tests were used for

Table 3. Detailed information on the patients with recurrent BOTs.

Case no.	Age (years)	Operation	Approach	Histology	Stage	Tumor size (cm)	Disease-free interval (mo)	Histology of recurrence	Treatment for recurrence	Disease status
1	36	Right salpingo-oophorectomy	MIS	Mucinous	Ic	17	13	BOT	Left ovarian cystectomy	NED
2	24	Left salpingo-oophorectomy	Laparotomy	Mucinous	Ia	17.5	23	BOT	Right oophorectomy	NED
3	38	Right salpingo-oophorectomy, pelvic lymph node dissection, omentectomy	Laparotomy	Mucinous	Ia	7	14	BOT	Hysterectomy, left salpingo-oophorectomy, chemotherapy	NED
4	28	Left ovarian cystectomy	MIS	Mucinous	Ic	3	29	BOT	Hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, omentectomy, chemotherapy	NED
5	22	Right salpingo-oophorectomy	MIS	Mucinous	Ia	10.5	25	BOT	Left ovarian cystectomy	NED
6	44	Bilateral salpingo-oophorectomy	MIS	Mucinous	Ib	11.6	40	N/A	Chemotherapy	NED

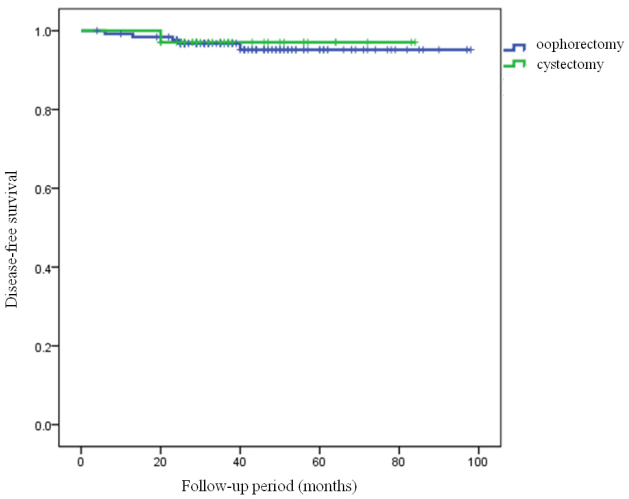

Fig. 3. The cumulative disease recurrence stratified by the type of surgery. During the mean follow-up period of 44 months, no difference was found in cumulative disease recurrence between the two groups ($p = 0.818$).

determining differences between the groups. The categorical variables were analyzed using a chi-square test or Fisher's exact test. The cumulative recurrence was calculated using the Kaplan–Meier method, and the log-rank test was used to confirm the statistical significance of differences between the groups. Disease-free survival (DFS) was calculated from the time of surgery to the presence of disease recurrence or the last date of follow-up with no evidence of disease. Cox proportional hazards for univariate analyses were conducted to confirm the risk factors for recurrence. Statistical significance was set at a p-value < 0.05. The Statistical Package for the Social Sciences version 22.0 (IBM Analytics, Armonk, NY, USA) was used for statistical analyses.

3. Results

3.1 Clinical characteristics of the study population

A total of 201 patients diagnosed with BOTs on pathology were identified; of them, 162 were enrolled in this study (Fig. 1). Thirty-four patients underwent an ovarian cystectomy, and 128 underwent an oophorectomy with or without salpingectomy. The patient demographics are shown in Table 1. The patients in the cystectomy group were younger than those in the oophorectomy group (29.2 years vs. 46.5 years, $p < 0.001$), and parity was higher in the oophorectomy group than in the cystectomy group (1.51 vs. 0.50, $p < 0.001$). There were no significant differences in body mass index ($p = 0.119$); however, the total hospital stay was longer in the oophorectomy group (8.75 days vs. 5.47 days, $p < 0.001$), while the proportion of patients who underwent MIS was higher in the cystectomy group (88.2% vs. 46.9%, $p < 0.001$). The trends associated with MIS for treating BOTs are shown in Fig. 2. The application of MIS dramatically increased starting in the year 2011. We have provided the full patient data in a **supplementary material**.

Table 4. Cox proportional hazards of disease-free survival in a univariate analysis.

	HR	95% CI	*p*-value
Age	0.955	0.901–1.013	0.129
Parity	0.912	0.441–1.887	0.805
BMI	0.876	0.689–1.114	0.282
Tumor size	0.950	0.842–1.072	0.405
Stage	0.048	0.000–3255.126	0.852
Serous histology	0.032	0.000–84.728	0.392
Type of operation			0.819
Oophorectomy	1	-	
Cystectomy	1.285	0.150–11.014	
Intraepithelial carcinoma			0.639
None	1	-	
Present	22.795	0.000–1080.700	
Tumor capsule			0.721
Intact	1	-	
Unintended rupture	21.641	0.000–4703.308	
Surgical approach			0.573
Laparotomy	1	-	
MIS	0.614	0.112–3.353	
Year of surgery			0.652
Before 2011	1		
2011 and after	1.481	0.269–8.167	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; MIS, minimally invasive surgery.

3.2 Surgical outcomes

Table 1 also shows the surgical outcomes of the two groups. Histologic findings showed the tumors were mostly serous and mucinous, and no statistically significant differences were found between the two groups ($p = 0.306$). The appearance of intraepithelial carcinoma was also not different between the groups ($p = 0.746$). However, unintended rupture of the tumor occurred more during cystectomy than during oophorectomy ($p < 0.001$), whereas the tumor size was significantly larger in the oophorectomy group than in the cystectomy group ($p < 0.001$).

Surgical outcomes according to the type of surgical approach were also compared. Nienty patients underwent MIS (84 by conventional laparoscopy and six by robotic-assisted laparoscopy), while the remaining 72 underwent laparotomy. Those who underwent MIS had shorter hospital stays (5.37 days vs. 11.43 days, $p < 0.001$) and smaller tumors (10.8 cm vs. 16.4 cm, $p < 0.001$) than did those who underwent laparotomy. Tumor rupture was relatively more common in the MIS group than in the laparotomy group (7.8% vs. 1.4%, $p = 0.077$); additionally, when the odds ratio was calculated only for those who underwent MIS, this increased risk of tumor rupture in the cystectomy group was found (Table 2). Four and two recurrences were reported in the MIS and laparotomy groups, respectively ($p = 0.694$).

3.3 Disease outcomes

Six patients (3.70%) showed recurrence during the follow-up period: one in the cystectomy group and five in the oophorectomy group. Detailed information on each of these patients is shown in Table 3. The mean follow-up period was 44 months, and the Kaplan–Meier curve analysis results did not show a difference in the DFS between the two groups ($p = 0.818$, log-rank test) (Fig. 3). The 2-year DFS rate was 97.1% in the cystectomy group and 97.6% in the oophorectomy group. None of the patients died in both groups. To identify possible risk factors of disease recurrence, a univariate analysis using Cox proportional hazards was performed, which failed to identify any risk factors for recurrent BOTs (Table 4).

4. Discussion

In this study, disease outcomes were comparable between ovarian cystectomy and oophorectomy for BOTs. As BOTs usually occur in young, fertile women, fertility preservation should be discussed during surgical planning. Fertility-sparing surgery is defined as a surgical approach meant to spare the uterus and one or both ovaries. Ovarian cystectomy has the benefit of potentially preserving fertility because of the greater residual ovarian tissue compared to that with oophorectomy. However, this requires a careful approach since survival and safety are as important as fertility.

In our study population, recurrent disease was reported in only six patients (3.70%) during their follow-up. This is consistent with the findings of previous study by Trillsch *et al.* [10], who reported a recurrence rate of 5%; however, the authors also stated that the rate of recurrence was higher after conservative management (10%–20%), and increased to 75% after cystectomy. Only one study has prospectively compared the outcomes between bilateral ovarian cystectomy and oophorectomy with contralateral cystectomy in patients with bilateral BOTs [11]. In that study, disease recurrence was not different between two groups; however, the time to first recurrence was significantly shorter in the bilateral cystectomy group than in the other group. However, no prospective study has evaluated the difference of disease outcome between cystectomy and oophorectomy in patients with BOTs.

Several studies have reported the safety and risk of recurrence with ovarian cystectomy for BOTs (Table 5, Ref. [12–27]). The definitive treatment for BOTs is surgery, whether it is fertility-sparing or not. Published data on the oncologic outcomes after cystectomy are limited and have mostly included very few patients. With regard to fertility-sparing surgery, some authors have considered fertility preservation in BOTs as a safe and feasible option [15]. Conversely, Helpman *et al.* [27] described a high risk of disease relapse following fertility preservation surgery. In their study, patients with unilateral oophorectomy and cystectomy both belonged to the same group and were com-

Table 5. Review of studies comparing fertility-sparing surgery for BOTs.

Authors	Total, n	Operation	n	Recurrence, n (%)	Disease-free interval (mo)	Death (n)	Follow-up period (mo)
Gotlieb *et al.* (1998) [12]	39	Cystectomy	12	2 (16.6%)	82.5	0	70
		Oophorectomy	27	2 (7.4%)	33		
Seracchioli *et al.* (2001) [13]	19	Cystectomy	11	1 (9%)	6	0	42
		Oophorectomy	8	0 (0%)			
Morice *et al.* (2001) [14]	44	Cystectomy	11	4 (36.3%)	-	0	109
		Oophorectomy	33	5 (15.1%)			
Zanetta *et al.* (2001) [15]	189	Cystectomy	50	14 (28%)	39	1	70
		Oophorectomy	139	21 (15.1%)	45		
Camatte *et al.* (2002) [16]	38	Cystectomy	21	4 (19%)	-	0	71
		Oophorectomy	47	5 (10.6%)			
Donnez *et al.* (2003) [17]	16	Cystectomy	5	1 (20%)	12	0	43.4
		Oophorectomy	11	2 (18.2%)	21		
Boran *et al.* (2005) [18]	62	Cystectomy	22	3 (13.6%)	24	0	44.3
		Oophorectomy	40	1 (2.5%)	48		
Romagnolo *et al.* (2006) [19]	53	Cystectomy	21	6 (28.6%)	-	1	44
		Oophorectomy	32	7 (21.9%)			
Wong *et al.* (2007) [20]	116	Cystectomy	38	2 (5.3%)	59*	1	21
		Oophorectomy	78	2 (2.3%)			
Yinon *et al.* (2007) [21]	62	Cystectomy	22	5 (22.5%)	23.6	0	88
		Oophorectomy	40	11 (27.5%)	41		
Park *et al.* (2009) [22]	184	Cystectomy	56	6 (10.7%)	10	1	70
		Oophorectomy	128	3 (2.3%)	49.5		
Kanat-Pektas *et al.* (2011) [23]	55	Cystectomy	19	2 (10.5%)	-	0	61
		Oophorectomy	36	1 (2.8%)			
Song *et al.* (2011) [24]	155	Cystectomy	38	5 (13.2%)	28	0	56
		Oophorectomy	117	7 (5.9%)	42		
Tsai *et al.* (2011) [25]	31	Cystectomy	7	5 (71%)	36.3	0	56.5
		Oophorectomy	24	2 (8.3%)	89.1		
Uzan *et al.* (2014) [26]	119	Cystectomy	69	26 (37.7%)	-	1	45
		Oophorectomy	50	12 (24%)			
Helpman *et al.* (2017) [27]	112	Cystectomy	60	50 (24%) *	-	11	75
		Oophorectomy	52				
This study	169	Cystectomy	35	2 (5.7%)	29.7	1	27.9
		Oophorectomy	134	6 (4.5%)	27.5		

*Groups not divided.

BOT, borderline ovarian tumor; mo, months.

pared to patients that underwent bilateral oophorectomy. Their study provided evidence for the feasibility of preserving fertility; however, it could not determine the safety of ovarian cystectomy for BOTs. Furthermore, the total recurrence rate was relatively higher (24%) than that found in other reports. This might have altered the statistical significance of Helpman *et al.*'s [27] findings. In the present study, we compared the safety of ovarian cystectomy with oophorectomy directly, to evaluate whether the tumor was completely and safely removed by cystectomy. Indeed, all types of surgery were included in the study population: cystectomy and oophorectomy with or without salpingectomy and even cytoreductive surgery. The recurrence rate was relatively low even after ovarian cystectomy (1/34, 2.9%).

A few studies have shown the safety of conservative surgery with favorable outcomes and similar survival rates even when compared with radical surgery [6,15,25]. The local relapse of BOTs found with conservative surgery is not considered to have an impact on invasive recurrence and has not been associated with decreased overall survival in

most studies. Whether the pattern of local recurrence is related to residual tumor in the same ovary or to tumor localization in the contralateral ovary is not clear; thus, special attention is required during ovarian cystectomy for BOTs. Conversely, indications for adjuvant treatment seem to be limited as neither randomized studies nor literature reviews have demonstrated adjuvant therapy improves survival, and it may even harm residual ovarian function and potentially decrease pregnancy outcomes.

There was no difference in disease outcomes between MIS and open laparotomy. The safety of MIS for borderline tumors is controversial. Two studies have reported more tumor ruptures and incomplete staging in laparoscopy resections than in MIS resections [28,29]. In addition, Bois *et al*. [30] reported an increased relapse rate after fertility-sparing surgery via laparoscopy compared to that via laparotomy. However, a multicenter study based in Europe reported no significant differences in the recurrence rate after MIS compared with laparotomy [19], and others have described a lower morbidity and less frequent adhesion for laparoscopic surgeries than for MIS [31].

Although the tumor rupture rate was higher for MIS than for laparotomy in our study, it did not appear to affect disease recurrence. Recently, some authors described that the risks of spilling contents can be reduced by the systematic use of an endoscopic bag and sufficient peritoneal irrigation [13,17]. However, it is difficult to reach a conclusion on this issue because there are currently no prospective studies. Nevertheless, MIS could be a feasible option for the surgical management of BOTs if performed by a skilled gynecologic oncologist with ample experience.

There were a few limitations to our study. First, there may have been a selection bias due to the retrospective study design. Patients who underwent oophorectomy were older and had relatively higher levels of CA-125 compared to those who underwent cystectomy. Second, this study was conducted at a single institution; thus, only a limited number of patients were included. Additionally, data on anti-Müllerian hormone levels were not collected for most of the patients, and the remnant ovaries' function after fertility-sparing surgery could not be evaluated. Therefore, further analysis should consider the risks and benefits of fertility-sparing surgery. Finally, pregnancy outcomes could not be analyzed due to the lack of data on pregnancy in most patients' medical records. Short follow-up periods are a common shortcoming when studying BOTs. While most studies report favorable survival rates, patients are typically followed-up for a short time (generally less than five years), and many patients are lost to follow-up before any pregnancy.

5. Conclusions

In conclusion, ovarian cystectomy can be a safe and effective option for the surgical management of BOTs and could be conducted via MIS with favorable outcomes. Ovarian cystectomy should be considered particularly for patients who wish to preserve fertility for childbearing potential. Further evaluations with a larger study population is warranted to evaluate the significant safety and efficacy of ovarian cystectomy in BOTs.

Abbreviations

BOTs, borderline ovarian tumors; CA-125, cancer antigen 125; DFS, disease-free survival; MIS, Minimally invasive surgery.

Author contributions

SK and JYS designed the research study. SK performed the research. KJM and SL provided assistance and advice on methodology. JHH, JKL, NWL, SL, and JYS provided patient data for the study. SK wrote the manuscript. JYS supervised all the research. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Data collection and analyses were approved by the ethical review board of our institution (No. 2018AN0319).

Acknowledgment

We would like to thank Editage (www.editage.co.kr) for English language editing.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/CEOG/49/2/10.31083/j.ceog4902051.

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