Staging Procedures Fail to Benefit to the Fertility-preserved Women with Borderline Ovarian Tumors: A Retrospective Analysis of 448 cases

Na Li
Sichuan University West China Second University Hospital
Jinhai Gou
Sichuan University West China Second University Hospital https://orcid.org/0000-0002-2706-8094
Lin Li
Sichuan University West China Second University Hospital
Xiu Ming
Sichuan University West China Second University Hospital
Ting Wenyi Hu
Sichuan University West China Second University Hospital
Zhengyu Li (2273473821@qq.com)

Research article

Keywords: Borderline Ovarian Tumour, Surgery Staging, Fertility-Sparing Surgery, Disease-Free Survival

Posted Date: January 30th, 2020

DOI: https://doi.org/10.21203/rs.2.22122/v2

Abstract

Purpose

The study is aimed to evaluate the potential effect of clinicopathologic and surgical factors on the prognosis and fertile outcomes in the patients with borderline ovarian tumors.

Patients and Methods

We performed a retrospective analysis involving BOT patients who had underwent surgical procedures in West China Second University Hospital from January 2008 to January 2015 . The disease-free survival (DFS) outcomes and potential prognostic factors were evaluated using Kaplan-Meier method and Cox regression analysis, respectively. Furthermore, the fertile outcomes were analyzed using Pearson X2 and Fish correlation test.

Results

A total of 448 patients were included with a median age of 37.1 years and a median follow-up time of 113 months. Forty-two (11.6%) recurrences with the mean recurrence interval 80.2 months and four (0.9%) deaths were observed. One hundred and eighteen (26.3%) patients were underwent staging surgery and the remaining 330 (73.7%) patents underwent unstaged surgery. A total of 233 patients undergoing fertility sparing surgery (FSS) attempted to conceive and 92 (39.48%) of them achieved pregnancy. No statistically significant difference of fertile outcomes were found between staging surgery group or not (P=0.691). In univariate analyse, staging surgery was obviously associated with DFS (HR=2.191 P=0.005), but was not an independent prognostic factor (p=0.600) for DFS on multivariate analysis. The multivariate Cox analysis revealed that advanced FIGO stage (≥stage II), positive ascites\pelvic washings and laparotomy approach were independent prognostic factors for DFS in overall patients, whereas advanced stage (≥stage II), laparotomy approach, cystectomy-included procedure, invasive implants and bilateral tumors were independent prognostic factors for DFS in patients undergoing FSS. In addition, laparoscopy approach had better prognosis than laparotomy in patients of early stage (stage I) with fertility desire.

Conclusion

Patients with BOT fail to benefit from surgical staging in prognosis and fertile outcomes. Laparoscopy will be recommended to patients of stage I with fertility desire. Patients with fertility desire at advanced stage (≥stage II), invasive implants and bilateral tumors should pay more attention to the risk of recurrence and choose FSS carefully.

Introduction

Borderline ovarian tumour (BOT) is a peculiar tumour type with a more favourable prognosis than that of malignant ovarian tumours. BOT typically occurs in women 10 years younger than those with epithelial

ovarian cancer (EOC), and the majority of women with BOT are diagnosed in earlier stages, with 75% of BOT diagnosed in Stage I [1, 2].

The clinical management of BOT has evolved over the past two decades as our understanding of its biological behaviour has been elucidated. Treatment is based on surgical removal of the tumour, with an emphasis on fertility sparing surgery (FSS) in women of childbearing age. The role of comprehensive surgical staging in the treatment of BOT is still controversial. Because peritoneal implants are a significant prognostic index and the most common sites of implants include the omentum and peritoneal surfaces, surgical staging that includes resection of the primary borderline tumour, abdominal/pelvic cytologic washings, omentectomy, and peritoneal biopsies is recommended. Routine lymphadenectomy is not recommended [3, 4]. However, considerations for comprehensive surgical staging, adequate tissue sampling, and adequate follow-up period are essential tools for gaining additional insight into optimal clinical management [2]. Previous studies have been inconsistent in their support of the benefits of staging surgery, and a recent systematic literature review found that staging surgery, including hysterectomy and lymphadenectomy for BOT, is not supported by the evidence [5–7]. As the chances of uterine or nodal metastasis are low in apparent early-stage BOT, the risk of surgical complications and the benefits of staging information must be weighed carefully.

Materials And Methods

The clinical data of patients with BOT were collected retrospectively in West China Second University Hospital between January 2008 and December 2015. Patients with a pathological diagnosis of BOT who underwent surgery were enrolled in this study. Those with concurrent ovarian cancer or other malignant reproductive tumours or without complete data were excluded. This study was approved by the Medical Ethics Committee of West China Second University Hospital. Data were retrieved from medical records and patient charts, including age, tumour size, lesion location, International Federation of Gynecology and Obstetrics (FIGO) stage, surgical approach, histological subtype, treatment with chemotherapy, and follow-up information. Additionally, obstetric and oncological outcomes were collected by medical record review, telephone interview, or out-patient interview. Although the FIGO ovarian staging classification was revised on January 1, 2014, we used the previous staging (2009) classification for consistency [8]. In addition, histological types were determined in accordance with the World Health Organization (WHO) system (2003). Histopathological information was obtained from pathological specimens, which were evaluated by two pathologists experienced in gynaecologic pathology. The tumours were divided into four histological types, including serous, mucinous, endometrioid, and serous/mucinous types. Micropapillary lesions were defined as a serous borderline tumour containing complex micropapillary structures. Microinvasion was defined as stromal invasion restricted to an area of no more than 10 mm^2 [9]. Several surgical operation types are mentioned in this study, such as FSS, which was performed to conserve the uterus and at least a portion of one ovary [10], and radical resection, which included total hysterectomy and bilateral salpingo-oophorectomy. Moreover, the concepts of three surgery types need to be clarified: complete staging, incomplete staging, and unstaged surgeries. Complete staging was defined

as peritoneal washing and/or biopsies, pelvic and para-aortic lymphadenectomy (sampling or systematic), and omentectomy. If peritoneal washing, omentectomy, and/or peritoneal biopsies without lymphadenectomy were performed, this was considered an incomplete staging surgery. The staging surgery group herein refers to those who received complete staging surgery. Furthermore, if only ovarian surgery (ovarian cystectomy or oophorectomy) was performed, this was considered an unstaged surgery [11]. Additionally, if patients underwent only an appendectomy with ovarian surgery, they were also classified in the unstaged group. Four types of fertility-sparing surgery are mentioned in this study, including unilateral salpingo-oophorectomy, unilateral cystectomy, bilateral cystectomy, and unilateral salpingo-oophorectomy plus contralateral cystectomy. The last three modalities were defined as cystectomy-included surgery. Patients were followed-up once every 3 months for the first 2 years, 6 months for years 3–5 after the surgery, and once per year thereafter. Gynaecological examination, abdominal ultrasonography, and tumour marker evaluation were recommended in each follow-up cycle. Based on the favourable prognosis, disease-free survival (DFS, defined as the duration from primary surgery to the first recurrence or the last visit) was used to assess oncological outcomes.

Statistical analysis of DFS, recurrence rate, and pregnancy rate were selected as the primary outcomes in this study. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) statistical software (version 20.0). The chi-square test and Student's t-test for unpaired data were used for statistical analysis. Survival analysis was based on the Kaplan Meier method, and the results were compared using the log-rank test. Univariate and multivariate Cox regression analysis were used to determine factors affecting recurrence presented as hazard ratios (HR). A P-Value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 448 patients with BOT were enrolled in this study. The demographics and clinicopathological characteristics are shown in *Table 1*.

The median age at diagnosis was 37.1 years (range: 11–82 years). The majority of patients were of FIGO stage I (n=347, 77.46%), whereas a few cases were of stage II (n=20, 4.46%), and the remaining were of stage III (n=74, 16.52%) and stage IV (n=7, 1.56%). The most common pathological type of BOT was serous (n=258, 57.59%), followed by mucinous (n=150, 33.48%), serous/mucinous (n=32, 7.14%), and endometrioid (n=8, 1.79%). Notably, most patients had unilateral lesions (n=352, 78.57%), whereas 96 (21.43%) patients had bilateral lesions. Among the patients enrolled, 81 (18.08%) had micropapillary lesions, 88 (19.64%) had microinvasion lesions, and 25 (5.58%) had carcinogenesis lesions.

Regarding surgical approach, 298 patients (66.52%) underwent laparotomy and 150 patients (33.48%) underwent laparoscopy. A total of 118 cases (26.34%) underwent complete staging surgery, whereas the rest underwent incomplete staging or unstaged surgery. Abdominal/pelvic washings or ascites were collected prior to the surgeries of all patients, and positive involvement was identified in 27 patients

(6.03%). Lymph node metastasis was detected in 21 patients among those who had lymphadenectomy (n=113). Appendix metastases were detected in 11 patients among those who underwent appendectomy (n=150). Omentum metastases were detected in 27 patients among those who underwent omentectomy (n=117). A total of 121 patients (27.01%) received adjuvant chemotherapy due to lymph node metastasis, positive abdominal/pelvic washings, invasive implants, and/or other high-risk indicators.

Oncological outcomes in patients with BOT

Survival analysis was performed; the median follow-up for this study was 113 (range: 14–166) months. At the last follow-up, 42 (11.6%) patients experienced recurrences, with a mean recurrence interval of 80.2 months and 4 (0.9%) disease-specific deaths were observed. The recurrence rate in patients who underwent incomplete staging/unstaged surgery (30/330, 9.09%) was lower than that in those receiving complete staging surgery (22/118, 18.64%), which was statistically significant (P<0.01). Results of univariate and multivariate analyses of DFS in all patients are shown in *Table 2*.

According to the univariate analysis, patients who received complete staging surgery had shorter DFS than those who underwent incomplete staging or unstaged surgery. In addition, laparoscopy was more associated with improved DFS (HR=0.292, 95% CI: 0.132–0.647, P=0.002) compared to laparotomy. Other factors were found to be associated with DFS, including FIGO stage, histology, lesion location, microinvasion, adjuvant chemotherapy, ascites/pelvic washings, cancer antigen (CA)-125 level, appendectomy, and invasive implants (all P<0.01). Micropapillary and carcinogenic lesions were not associated with DFS (P>0.05).

Although several factors were found to be associated with DFS by univariate analysis, only three of them, including FIGO stage (OR: 6.544, 95%: 2.137–20.041), positive ascites/pelvic washings (OR: 3.259, 95% CI: 1.202–8.835), and surgical approach (OR: 0.319, 95% CI: 0.128–0.793), were identified as factors significantly associated with DFS (P<0.001, P=0.014, P=0.043, respectively) by multivariate analysis. However, complete staging surgery was not associated with DFS (P=0.600) according to the multivariate analysis. There was no difference in DFS found between patients who underwent either FSS or radical surgery by both univariate and multivariate analyses.

Subgroup analysis showed that, in patients who underwent complete staging surgery, there was no difference in DFS between those who received either laparotomy or laparoscopy (p=0.349). In patients who underwent incomplete staging/unstaged surgery, the DFS in patients who underwent laparoscopy was longer than in those who underwent laparotomy (P=0.011; *Supplementary Table 1*).

Oncological outcomes in patients with BOT after FSS

Among the patients enrolled, 270 patients underwent FSS. Of these, 32 patients (11.8%) experienced recurrence. To explore the potential risk factors associated with improved DFS in patients who underwent FSS, univariate and multivariate analyses were performed, shown in *Table 3*.

Univariate analysis in patients with FSS revealed that patients who underwent complete staging surgery had shorter DFS than those who underwent incomplete staging or unstaged procedures (OR: 4.290, 95% CI: 1.979–9.298, *P*<0.001). When compared to those who underwent laparotomy, DFS in patients who underwent laparoscopy was improved (OR: 0.332, 95% CI: 0.135–0.820, *P*=0.017). In addition, patients who underwent salpingo-oophorectomy had longer DFS than those who underwent a cystectomy-included procedure (OR: 0.230, 95% CI: 0.168–0.867, *P*=0.021). Other factors were also associated with DFS in patients who underwent FSS, including FIGO stage, histology, lesion location, microinvasion, adjuvant chemotherapy, positive ascites/pelvic washings, appendectomy, and invasive implants *(P*<0.05).

In the multivariate analysis, there was no difference in DFS between patients who underwent complete or incomplete/unstaged surgery *(P*=0.358). No difference in DFS was found between patients with different histological types. Early FIGO stage (OR: 11.586, 95% CI: 4.535–29.602), unilateral lesions (OR: 2.581, 95% CI: 1.061–6.283), laparoscopy (OR: 0.367, 95% CI: 0.148–0.913), salpingo-oophorectomy (OR: 0.367, 95% CI: 0.148–0.913), and no invasive implants (OR: 4.832, 95% CI: 1.663–14.037) were independent factors for improved DFS (p<0.05).

Reproductive outcomes in patients with BOT after FFS

At the last follow-up, of 270 patients who underwent FSS, 252 patients had attempted to conceive and 92 had achieved pregnancy. The correlation between clinicopathological characteristics and reproductive outcome is shown in *Table 4*. The pregnancy rate in patients aged <35 years was higher than those aged ≧35, and was statistically significant *(P*<0.001). Of 30 patients who underwent complete staging surgery, 13 patients succeeded in conceiving, whereas 79 of 203 patients who underwent incomplete/unstaged surgery succeeded in conceiving, but these differences were not statistically significant *(P*>0.05). There was no difference between patients who received either laparotomy or laparoscopy. Similarly, in patients who underwent salpingo-oophorectomy or cystectomy, there was no difference in pregnancy rate *(P*>0.05).

Discussion

In the present study, we performed a retrospective analysis of 448 patients with BOT in a single centre in China. BOT are a group of ovarian neoplasms with characteristics between benign and malignant, frequently occurring in young women, and is associated with favourable prognosis. Within the past two decades, we have begun to understand the biological behaviour of BOT; however, the optimal therapy for this disease is still controversial. Numerous studies have focused on the oncological and reproductive outcomes of BOT. In the literature, the primary points of discussion regarding BOT include the prognostic factors for overall surivival (OS) or DFS, the necessity of staging surgery, the application of minimally invasive approach, and the outcome of conservative surgery.

Complete staging surgery generally includes resection of the primary borderline tumour (cystectomy or salpingo-oophorectomy), cytologic washings, omentectomy, peritoneal biopsies and routine

lymphadenectomy. Unlike in ovarian cancer, previous studies have shown that the prognosis of patients with BOT is generally favourable, with very low mortality [12, 13]. A Turkish Gynaecologic Oncology Group (GOG) study showed that the five-year survival rate of patients with BOT was 100% and the median survival time was 120 months [14]. Therefore, DFS and recurrence-free survival (RFS) was defined as the main oncological outcomes. In the present study, complete staging surgery was performed in 26.3% of patients. Although univariate analysis showed that patients who underwent complete staging surgery had shorter DFS than those who underwent incomplete staging/unstaged surgery, no significant difference was found in DFS between these surgical approaches by multivariate analysis. These results were similar to those previous studies [2, 11, 14–16]. The GOG study in Turkish showed that comprehensive surgical staging did not lead to any difference in survival [14]. A retrospective multicentre study showed that there were no differences in 5-year RFS and OS between patients with or without complete surgical staging [17]. Another multicentre study showed that surgical staging, including lymph node sampling or dissection, appendectomy, and hysterectomy, were not beneficial in the management of BOT [11]. A third multicentre study from Turkey that focused on mucinous BOT also showed that radical surgery, omentectomy, appendectomy, and lymphadenectomy were not independent prognostic factors for progression-free survival (PFS) and OS [16].

Regarding the correlation between lymphadenectomy and DFS, lymph node involvement does not appear to be a prognostic factor [18, 19]. Univariate analysis by Matsuo et al. showed that surgical staging patterns for hysterectomy and lymphadenectomy were not associated with cause-specific survival (P = 0.19) [2]. A previous study by Qian et al. showed that there were no significant differences between groups who either had lymphatic node involvement or did not (p = 0.778), and between patients who had either more or fewer than ten nodes removed (P = 0.549) [15].

BOT occurs in women of all ages, with the average age of onset in the mid-40 s; therefore, a high proportion of women with BOT are in the reproductive age group [20]. In the present study, the median age at diagnosis was 37.1 years. Therefore, a conservative surgical approach, especially FSS, was the preferred choice for patients at a reproductive age who desired to preserve fertility. However, the balance between oncological and reproductive outcomes should be assessed adequately; approximately 12–36% of patients with BOT who undergo FSS experience recurrence [20], and the most common site of recurrence is in the residual ovary [20–23]. Previous studies have shown that the recurrence rate of BOT in patients who underwent FSS was markedly higher than that in patients who received radical surgeries (21.4% vs 6.3%, P < 0.05) [9, 24]. Furthermore, a proportion of patients who underwent FSS were found to experience an invasive recurrence [13]. Regarding surgical patterns, meta-analysis revealed that unilateral cystectomy is significantly associated with higher recurrence rates [10]. However, another study reported that there was no statistically significant difference between patients who underwent either cystectomy or unilateral salpingo-oophorectomy [25]. A recent study including 6295 patients showed that FSS was associated with worse disease-specific survival in patients ≥ 50 years of age, but not in those < 50 years of age [26]. Another study also showed that surgical procedure (conservative vs. radical) was not an independent prognostic factor for DFS or OS [11]. In the present study, univariate and multivariate analyses both showed that there was no significant difference in DFS between patients who either

underwent FSS or did not (P > 0.05). In patients who received FSS, there was no significant difference in DFS between those who either received complete staging or did not (P > 0.05), whereas a significant difference was seen between laparoscopy and laparotomy (P < 0.05). However, no significant differences in reproductive rate were found between those who underwent either surgery staging or a different surgical approach. Therefore, one should give extra consideration to the balance between oncological and reproductive outcomes in patients of a reproductive age before performing FSS.

The standard treatment for BOT is surgery. Because most patients are of a young age, surgeons should consider using a minimally invasive procedure. Laparoscopic surgery has several advantages over open surgery in the management of gynaecologic diseases, including fewer peri-operative complications and superior cosmetic outcomes. In this study, approximately 33.48% patients underwent laparoscopy. By both univariate and multivariate analyses, laparoscopy was more positively associated with improved DFS than laparotomy (P < 0.05). Similarly, a previous study by Song et al. also showed that RFS and OS did not differ between the laparoscopy (single-port and multi-port laparoscopy) and laparotomy groups [27].

In a retrospective study of 1069 patients with BOT in Japan, 49% had normal serum CA-125 levels and only 23% had serum CA-125 levels above 100 U/ml [20]. In another study of 198 patients with pre-operative serum CA-125 data conducted in Singapore, 77 (39%) had levels > 35 U/ml [28]. In the present study, the level of CA-125 was not an independent prognostic factor for patients with BOT after FSS.

Because an accurate intra-operative diagnosis is important in the management of BOT, frozen section examination should be performed to help surgeons and patients' families make decisions during intra-operative periods. The accuracy of frozen-section examination is lower than optimal and the availability of reliable frozen-section analysis in many hospitals is problematic. Previous studies have shown that the matched rate between frozen-section and definitive histological result varies from 66.67–88.9% [29, 30]. Therefore, it is important for surgeons to counsel patients and their families appropriately with regard to intra-operative management.

Conclusions

Patients with BOT do not benefit from surgical staging procedures in terms of prognosis and fertility outcomes. Laparoscopy, rather than laparotomy, should be recommended for patients with stage I disease who wish to preserve their fertility. In addition, patients with advanced-stage disease, invasive implants, and/or bilateral tumours who wish to maintain fertility should consider the risk of recurrence before choosing FSS. Unilateral salpingo-oophorectomy is an alternative method for patients with BOT to preserve fertility.

Declarations

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. Fischerova D, Zikan M, Dundr P, Cibula D: **Diagnosis, treatment, and follow-up of borderline ovarian tumors**. *Oncologist* 2012, **17**(12):1515-1533.
2. Matsuo K, Machida H, Takiuchi T, Grubbs BH, Roman LD, Sood AK, Gershenson DM: **Role of hysterectomy and lymphadenectomy in the management of early-stage borderline ovarian tumors**. *Gynecologic oncology* 2017, **144**(3):496-502.
3. Gershenson DM, Silva EG, Tortolero-Luna G, Levenback C, Morris M, Tornos C: **Serous borderline tumors of the ovary with noninvasive peritoneal implants**. *Cancer* 1998, **83**(10):2157-2163.
4. Fotopoulou C, Schumacher G, Schefold JC, Denkert C, Lichtenegger W, Sehouli J: **Systematic evaluation of the intraoperative tumor pattern in patients with borderline tumor of the ovary**. *Int J Gynecol Cancer* 2009, **19**(9):1550-1555.
5. Menczer J, Chetrit A, Sadetzki S, National Israel Ovarian Cancer G: **The effect of hysterectomy on survival of patients with borderline ovarian tumors**. *Gynecologic oncology* 2012, **125**(2):372-375.
6. Shazly SA, Laughlin-Tommaso SK, Dowdy SC, Famuyide AO: **Staging for low malignant potential ovarian tumors: a global perspective**. *American journal of obstetrics and gynecology* 2016, **215**(2):153-168 e152.
7. Messalli EM, Grauso F, Balbi G, Napolitano A, Seguino E, Torella M: **Borderline ovarian tumors: features and controversial aspects**. *European journal of obstetrics, gynecology, and reproductive biology* 2013, **167**(1):86-89.
8. Petru E, Luck HJ, Stuart G, Gaffney D, Millan D, Vergote I, Gynecologic Cancer I: **Gynecologic Cancer Intergroup (GCIG) proposals for changes of the current FIGO staging system**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **143**(2):69-74.
9. Fang C, Zhao L, Chen X, Yu A, Xia L, Zhang P: **The impact of clinicopathologic and surgical factors on relapse and pregnancy in young patients (</=40 years old) with borderline ovarian tumors**. *BMC cancer* 2018, **18**(1):1147.
10. Jiao X, Hu J, Zhu L: **Prognostic Factors for Recurrence After Fertility-Preserving Surgery in Patients With Borderline Ovarian Tumors: A Systematic Review and Meta-analysis of Observational Studies**. *Int J Gynecol Cancer* 2017, **27**(9):1833-1841.
11. Gokcu M, Gungorduk K, Asicioglu O, Cetinkaya N, Gungor T, Pakay G, Cuylan ZF, Toptas T, Ozyurt R, Agacayak E *et al*: **Borderline ovarian tumors: clinical characteristics, management, and outcomes - a multicenter study**. *Journal of ovarian research* 2016, **9**(1):66.
12. Lou T, Yuan F, Feng Y, Wang S, Bai H, Zhang Z: **The safety of fertility and ipsilateral ovary procedures for borderline ovarian tumors**. *Oncotarget* 2017, **8**(70):115718-115729.
13. Zanetta G, Rota S, Chiari S, Bonazzi C, Bratina G, Mangioni C: **Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective**

study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2001, **19**(10):2658-2664.

14. Guvenal T, Dursun P, Hasdemir PS, Hanhan M, Guven S, Yetimalar H, Goksedef BP, Sakarya DK, Doruk A, Terek MC *et al*: **Effect of surgical staging on 539 patients with borderline ovarian tumors: a Turkish Gynecologic Oncology Group study**. *Gynecologic oncology* 2013, **131**(3):546-550.
15. Qian XQ, Hua XP, Wu JH, Shen YM, Cheng XD, Wan XY: **Clinical Predictors of Recurrence and Prognostic Value of Lymph Node Involvement in the Serous Borderline Ovarian Tumor**. *Int J Gynecol Cancer* 2018, **28**(2):279-284.
16. Gungorduk K, Asicioglu O, Braicu EI, Almuheimid J, Gokulu SG, Cetinkaya N, Gungor T, Pakay G, Telli EU, Cuylan ZF *et al*: **The Impact of Surgical Staging on the Prognosis of Mucinous Borderline Tumors of the Ovaries: A Multicenter Study**. *Anticancer research* 2017, **37**(10):5609-5616.
17. Bendifallah S, Nikpayam M, Ballester M, Uzan C, Fauvet R, Morice P, Darai E: **New Pointers for Surgical Staging of Borderline Ovarian Tumors**. *Annals of surgical oncology* 2016, **23**(2):443-449.
18. Longacre TA, McKenney JK, Tazelaar HD, Kempson RL, Hendrickson MR: **Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (> or =5-year) follow-up**. *The American journal of surgical pathology* 2005, **29**(6):707-723.
19. Lesieur B, Kane A, Duvillard P, Gouy S, Pautier P, Lhomme C, Morice P, Uzan C: **Prognostic value of lymph node involvement in ovarian serous borderline tumors**. *American journal of obstetrics and gynecology* 2011, **204**(5):438 e431-437.
20. Gershenson DM: **Management of borderline ovarian tumours**. *Best practice & research Clinical obstetrics & gynaecology* 2017, **41**:49-59.
21. Yinon Y, Beiner ME, Gotlieb WH, Korach Y, Perri T, Ben-Baruch G: **Clinical outcome of cystectomy compared with unilateral salpingo-oophorectomy as fertility-sparing treatment of borderline ovarian tumors**. *Fertility and sterility* 2007, **88**(2):479-484.
22. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH: **Surgical management of borderline ovarian tumors: The role of fertility-sparing surgery**. *Gynecologic oncology* 2009, **113**(1):75-82.
23. Song T, Choi CH, Park HS, Kim MK, Lee YY, Kim TJ, Lee JW, Bae DS, Kim BG: **Fertility-sparing surgery for borderline ovarian tumors: oncologic safety and reproductive outcomes**. *Int J Gynecol Cancer* 2011, **21**(4):640-646.
24. Sun L, Li N, Song Y, Wang G, Zhao Z, Wu L: **Clinicopathologic Features and Risk Factors for Recurrence of Mucinous Borderline Ovarian Tumors: A Retrospective Study With Follow-up of More Than 10 Years**. *Int J Gynecol Cancer* 2018, **28**(9):1643-1649.
25. Song T, Hun Choi C, Lee YY, Kim TJ, Lee JW, Bae DS, Kim BG: **Oncologic and reproductive outcomes of cystectomy compared with oophorectomy as a treatment for borderline ovarian tumours**. *Human reproduction* 2011, **26**(8):2008-2014.
26. Sun H, Chen X, Zhu T, Liu N, Yu A, Wang S: **Age-dependent difference in impact of fertility preserving surgery on disease-specific survival in women with stage I borderline ovarian tumors**. *Journal of ovarian research* 2018, **11**(1):54.

27. Song T, Kim MK, Jung YW, Yun BS, Seong SJ, Choi CH, Kim TJ, Lee JW, Bae DS, Kim BG: **Minimally invasive compared with open surgery in patients with borderline ovarian tumors**. *Gynecologic oncology* 2017, **145**(3):508-512.
28. Wong HF, Low JJ, Chua Y, Busmanis I, Tay EH, Ho TH: **Ovarian tumors of borderline malignancy: a review of 247 patients from 1991 to 2004**. *Int J Gynecol Cancer* 2007, **17**(2):342-349.
29. Yoshida A, Tavares BVG, Sarian LO, Andrade L, Derchain SF: **Clinical Features and Management of Women with Borderline Ovarian Tumors in a Single Center in Brazil**. *Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia* 2019, **41**(3):176-182.
30. Koensgen D, Weiss M, Assmann K, Brucker SY, Wallwiener D, Stope MB, Mustea A: **Characterization and Management of Borderline Ovarian Tumors - Results of a Retrospective, Single-center Study of Patients Treated at the Department of Gynecology and Obstetrics of the University Medicine Greifswald**. *Anticancer research* 2018, **38**(3):1539-1545.

Tables

Table 1
Demographics of patients with borderline ovarian tumors

	Non-staging surgery	Staging surgery	P Valve
Total	330	118	
Age (y,mean±Std)	36.75±14.35	38.03±12.49	0.363
Time of operation(h, mean)	127.50	255.00	0.000
Blood Loss (ml, median)	80	400	0.000
Length of stay(d, median)	6	8	0.000
FIGO Stage			
I	287 (87%)	60 (50.8%)	0.000
II	8 (2.40%)	12 (10.2%)	
III	32 (9.7%)	42 (35.6%)	
IV	3 (0.9%)	4 (3.4%)	
Histology			0.038
Serous	177 (53.6%)	81 (68.6%)	
Mucinous	119 (36.1%)	31 (26.3%)	
Endometrioid	7 (2.1%)	1 (0.8%)	
Serous and Mucinous	27 (8.2%)	5 (4.2%)	
Lesion lateral			0.000
Unilateral	277 (83.9%)	75 (63.6%)	
Bilateral	53 (16.1%)	43 (36.4%)	
Micropapillary			
Yes	45 (13.6%)	36 (30.5%)	0.000
No	285 (86.4%)	82 (69.5%)	
Microinvasion			0.000
Yes	31 (9.4%)	57 (48.3%)	
No	299 (90.6%)	61 (51.7%)	
Carcinogenesis			
Yes	14 (4.2%)	11 (9.3%)	0.058
No	316 (95.8%)	107 (90.7%)	
Surgical Approach			0.000
Laparotomy	192 (58.2%)	106 (89.8%)	
Laparoscopy	138 (41.8%)	12 (10.2%)	
Ascites/Cytologic washings			0.012
Positive	14 (4.2%)	13 (11.0%)	
Negative	316 (95.8%)	105 (89.0%)	
Lymph node involvement			NA
Yes	NA	21 (18.6%)	
No	NA	92 (81.4%)	
Appendix metastasis			
Yes	6 (54.5%)	5 (45.5%)	0.05
No	113 (81.3%)	26 (18.7%)	
Omentum metastasis			NA
Yes	NA	27 (23.1%)	
No	NA	90 (76.9%)	

ıdjuvant chemotherapy			0.000
Yes	54 (16.4%)	67 (56.8%)	
No	276 (83.6%)	51 (43.2%)	
ŧecurrence			0.007
Yes	30 (9.1%)	22 (18.6%)	
No	300 (90.9%)	96 (81.4%)	
ˈertility-sparing surgery			0.000
Yes	240 (72.7%)	30 (25.4%)	
No	90 (27.3%)	88 (74.6%)	
ıchieving pregnancy			0.552
Yes	79 (35.7%)	13 (41.9%)	
No	142 (64.3%)	18 (58.1%)	

Data were recorded as number (%), mean (±SD), or median (range).
Abbreviations: y, years; h, hours; d, days;

Table 2 Univariate and multivariate analysis of DFS

		Univariate		P value	Multivariate		P value
		HR	95% confidence interval		HR	95% confidence interval	
FIGO Stage	I	1					
	≧II	7.204	4.093-12.680	0.000	6.544	2.137-20.041	0.001
Histology	Serous	1					0.528
	Mucinous	0.353	0.171-0.726	0.005	1.215	0.275-5.375	0.797
	Others	0.286	0.069-1.183	0.084	0.632	0.130-3.066	0.569
Lesion lateral	Unilateral	1					
	Bilateral	2.554	1.460-4.469	0.001	1.076	0.526-2.202	0.840
Micropapillary	Yes	1.557	0.831-2.917	0.167			
	No	1					
Microinvasion	Yes	5.092	2.954-8.779	0.000	0.478	0.181-1.261	0.136
	No	1					
Carcinogenesis	Yes	1.049	0.327-3.366	0.936			NA
	No	1					
Staging surgery	Yes	2.191	1.263-3.801	0.005	0.810	0.393-1.669	0.567
	No	1					
Adjuvant chemotherapy	Yes	5.281	3.002-9.289	0.000	2.031	0.913-4.519	0.083
	No	1					
Ascites/Pelvic washings	Positive	5.442	2.850-10.391	0.000	3.259	1.202-8.835	0.020
	Negative	1					
Surgical Approach	laparotomy	1					
	laparoscopy	0.292	0.132-0.647	0.002	0.319	0.128-0.793	0.014
CA-125	Normal	1					
	Elevated	2.201	1.224-3.960	0.008	0.825	0.422-1.611	0.572
Fertility sparing surgery	No	1					
	Yes	1.055	0.063-1.845	0.851			NA
Appendectomy	No	1					
	Yes	0.394	0.192-0.808	0.011			NA
Invasive implants	NO	1					
	Yes	4.105	2.222-7.583	0.000	0.566	0.208-1.539	0.265

Table 3
Univariate and multivariate analysis of DFS in fertility desiring patients after fertility-sparing surgery

		Univariate		P Value	Multivariate		P Value
		OR	95% confidence interval		OR	95% confidence interval	
FIGO Stage	I	1					
	≧II	21.061	9.662-45.909	0.000	11.586	4.535-29.602	**0.000**
Histology	Serous	1		0.010			0.155
	Mucinous	0.196	0.068-0.654	0.003			0.189
	others	0.000		0.975			NA
Lesion lateral	unilateral	1					
	Bilateral	5.491	2.570-11.73	0.000	2.581	1.061-6.283	0.037
Micropapillary	Yes	1.976	0.840-4.649	0.119			NA
	No	1					
Microinvasion	Yes	14.644	6.940-30.903	0.000			0.955
	No	1					
Carcinogenesis	Yes	0.609	0.083-4.483	0.626			NA
	No	1					
Staging surgery	Yes	4.290	1.979-9.298	0.000			0.358
	No	1					
Adjuvant chemotherapy	Yes	7.797	3.648-16.664	0.000			0.391
	No	1					
Ascites/Pelvic washings	Positive	13.350	5.612-31.770	0.000			0.888
	Negative	1					
Surgical Approach	laparotomy	1					
	laparoscopy	0.332	0.135-0.820	0.017	0.367	0.148-0.913	0.031
CA-125	Normal	1					
	Elevated	1.649	0.748-3.632	0.215			NA
Fertility sparing surgery	Cystectomy-included	1					
	Adnexectomy	0.382	0.168-0.867	0.021	0.367	0.148-0.913	0.014
Appendectomy	No	1					
	Yes	0.240	0.083-0.692	0.008			0.189
Invasive implants	NO	1					
	Yes	14.289	6.400-31.902	0.000	4.832	1.663-14.037	0.004

Table 4
Correlation between pregnant outcomes and clinicopathological indexes in patients after fertility-sparing surgery

		Fertility outcome		P valvue
		No (n,%)	Yes (n,%)	
Staging surgery	No	124(87.9)	79(85.9)	0.691
	Yes	17(12.1)	13(14.1)	
Surgical approach	laparoscopy	65(46.1)	37(40.2)	0.419
	laparotomy	76(53.9)	55(59.8)	
Surgical procedure	Cystectomy	76(53.9)	41(44.6)	0.181
	Salpingo-oophorectomy	65(46.1)	51(55.4)	
Adjuvant chemotherapy	No	110(78.0)	77(83.7)	0.316
	Yes	31(22.0)	15(16.3)	
FIGO Stage	I	121(85.8)	84(91.3)	0.225
	≧II	20(14.2)	8(8.7)	
Histology	Serous	79(56.0)	39(42.4)	0.08
	Mucinous	47(33.3)	44(47.8)	
	others	15(10.6)	9(9.8)	
Lesion lateral	unilateral	122(86.5)	82(89.1)	0.686
	Bilateral	19(13.5)	10(10.9)	
Micropapillary	No	23(16.3)	12(13.0)	0.576
	Yes	118(83.7)	80(87.0)	
Microinvasion	No	126(89.4)	85(92.4)	0.499
	Yes	15(10.6)	7(7.6)	
Carcinogenesis	No	134(95.0)	86(93.5)	0.771
	Yes	7(5.0)	6(6.5)	
Ascites/Pelvic washings	Positive	7(5.0)	3(3.3)	0.744
	Negative	134(95.0)	89(96.7)	
CA-125	Normal	82(65.6)	60(69.8)	0.553
	Elevated	43(34.4)	26(30.2)	
nvasive implants	No	132(93.6)	88(95.7)	0.574
	Yes	9(6.4)	4(4.3)	
Age	<35	107(75.9)	92(100)	0.000
	≧35	34(24.1)	0	

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.doc