ANTICANCER RESEARCH *37*: 5609-5616 (2017)
doi:10.21873/anticanres.11995

# The Impact of Surgical Staging on the Prognosis of Mucinous Borderline Tumors of the Ovaries: A Multicenter Study

KEMAL GUNGORDUK[1], OSMAN ASICIOGLU[2], ELENA IOANA BRAICU[3], JUMANA ALMUHEIMID[3], SEVKI GOKSUN GOKULU[4], NILUFER CETINKAYA[5], TAYFUN GUNGOR[6], GONCA PAKAY[7], ELCIN UZMEZ TELLI[8], ZELIHA FIRAT CUYLAN[6], TAYFUN TOPTAS[9], AHMET BILGI[4], RAMAZAN OZYURT[10], ELIF AGACAYAK[11], AYKUT OZDEMIR[12], NURI YILDIRIM[4], SALIH TASKIN[13], TUFAN OGE[8], ONUR EROL[14], LEVENT AKMAN[4], ANIL TURAN[15], MEHMET SAIT ICEN[11], TAYLAN SENOL[7], OZLEM IRAK OVALI[13], BURCU YUCESOY[11], OZGU GUNGORDUK[1], OSMAN TEMIZKAN[16], MUZAFFER SANCI[17], TAYUP SIMSEK[9], MEHMET MUTLU MEYDANLI[6], MEHMET HARMA[15], LEVENT YASAR[12], AYSEL DERBENT UYSAL[14], ATES KARATEKE[7], FIRAT ORTAC[13], SABIT SINAN OZALP[8], JALID SEHOULI[3] and MUSTAFA ZELAL MUALLEM[3]

*[1]Department of Gynecology and Gynecologic Oncology, Mugla Education and Research Hospital, Mugla, Turkey;*
*[2]Department of Gynecology and Gynecologic Oncology, Kanuni Sultan Süleyman Education and Research Hospital, Istanbul, Turkey;*
*[3]Department of Gynecology with Center for Oncological Surgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany;*
*[4]Department of Gynecology and Gynecologic Oncology, Ege University School of Medicine, Izmir, Turkey;*
*[5]Department of Gynecology and Gynecologic Oncology, Trabzon Education and Research Hospital, Trabzon, Turkey;*
*[6]Department of Gynecology and Gynecologic Oncology, Zekai Tahir Burak Education and Research Hospital, Ankara, Turkey;*
*[7]Department of Gynecology and Gynecologic Oncology, Zeynep Kamil Education and Research Hospital, Istanbul, Turkey;*
*[8]Department of Gynecology and Gynecologic Oncology, Osmangazi University School of Medicine, Eskisehir, Turkey;*
*[9]Department of Gynecology and Gynecologic Oncology, Akdeniz University School of Medicine, Antalya, Turkey;*
*[10]Department of Gynecology and Gynecologic Oncology, Istanbul Education and Research Hospital, Istanbul, Turkey;*
*[11]Department of Gynecology and Gynecologic Oncology, Dicle University School of Medicine, Diyarbakır, Turkey;*
*[12]Department of Gynecology and Gynecologic Oncology, Bakırköy Sadi Konuk Education and Research Hospital, Istanbul, Turkey;*
*[13]Department of Gynecology and Gynecologic Oncology, Ankara University School of Medicine, Ankara, Turkey;*
*[14]Department of Gynecology and Gynecologic Oncology, Antalya Education and Research Hospital, Antalya, Turkey;*
*[15]Department of Gynecology and Gynecologic Oncology, Zonguldak Bulent Ecevit University School of Medicine, Zonguldak, Turkey;*
*[16]Department of Gynecology and Gynecologic Oncology, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey;*
*[17]Department of Gynecology and Gynecologic Oncology, Izmir Tepecik Education and Research Hospital, Izmir, Turkey*

*Correspondence to:* Dr. med. Dr. (syr.) Mustafa Zelal Muallem, Charité University Medicine Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450664373, Fax: +49 30450564900, e-mail: Mustafa-Zelal.Muallem@charite.de

*Key Words:* Mucinous borderline ovarian tumors, surgical staging, appendectomy, radical surgery.

**Abstract.** *Background/Aim: The purpose of this study was to prove the effect of complete surgical staging of patients with mucinous borderline ovarian tumors (mBOTs) especially appendectomy on progression-free survival (PFS) and overall survival (OS). Patients and Methods: The database of 14 gynecological oncology departments from Turkey and Germany were comprehensively searched for*

*women who underwent primary surgery for an ovarian tumor between January 1, 1998, and December 31, 2015, and whose final diagnosis was mBOT. Results: A total of 364 patients with mBOT with a median age of 43.1 years were included in this analysis. The median OS of all patients was 53.1 months. The majority of cases had Stage IA (78.6%). In univariate and multivariate analyses, radical surgery, omentectomy, appendectomy, lymphadenectomy, and adding adjuvant chemotherapy were not independent prognostic factors for PFS and OS. Furthermore, FIGO stage (≥IC vs. <IC), radical surgery, and staging surgery were not independent risk factors for recurrence of mBOTs. Finally, abnormal macroscopic appendix and FIGO stage (≥IC vs. <IC) were independent risk factors for appendiceal involvement (p=0.032). Conclusion: Patients with conservative surgery do not have higher recurrence rates. Fertility-sparing surgery should be considered in the reproductive age group. Detailed surgical staging including lymphadenectomy, appendectomy, and omentectomy does not have an impact on survival rates.*

Borderline ovarian tumors (BOTs) account for 10-20% of ovarian malignancies (1). The World Health Organization (WHO) ascribed the name "borderline" to these tumors, with morphological criteria (especially having a higher proliferative activity than benign neoplasms but having no stromal invasion) (2). Mucinous borderline ovarian tumor (mBOT) accounts for up to 30-50% of BOTs (3). For a long time, mBOT was divided into "intestinal" or "Mullerian" (endocervical) types. However, in accordance with a new classification, intestinal mBOT is accepted as mBOT and the endocervical type is considered a seromucinous tumor (4).

The optimal treatment approach in patients with mBOTs is still controversial. Some surgeons perform complete staging surgery because of the low accuracy and sensitivity of frozen section analysis in these patients, while others prefer conservative surgery (5, 6). In addition, over the years, guidelines often recommended removal of the appendix in patients with mBOT; however, appendectomy is controversial today, and some authors suggest appendectomy only if the appendix appears macroscopically abnormal (3, 7-10).

The goal of this study was to prove the effect of complete surgical staging of patients with mucinous borderline ovarian tumors (mBOTs) especially appendectomy on progression-free survival (PFS) and overall survival (OS).

## Materials and Methods

This retrospective study was carried out using 14 gynecological oncology department databases from Turkey and Germany. All patients with mBOTs diagnosed between January 1, 1998, and December 31, 2015, were included. This study was approved by the local ethics committee (EK207/2003). It was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Table I. *Demographic, pathological, and surgical characteristics of patients with mucinous borderline ovarian tumors.*

| Characteristic | N=364 |
|---|---|
| Age | |
| Median (n: range in years) | 43.1 (16-87) |
| Postmenopausal status (n, %) | 118 (32.4) |
| Ultrasound image (n, %) | |
| Solid | 53 (14.5) |
| Cystic | 71 (19.5) |
| Not reported | 240 (65.9) |
| Median CA-125 level (U/mL) | 137 (1-8553) |
| Median tumor diameter (mm) | 113.25±72.57 |
| FIGO stage at diagnosis (n, %) | |
| IA | 286 (78.6) |
| IB | 16 (4.4) |
| IC | 26 (6.6) |
| IIA | 0 (0.0) |
| IIB | 0 (0.0) |
| IIC | 0 (0.0) |
| IIIA | 23 (6.3) |
| IIIB | 1 (0.3) |
| IIIC | 14 (3.8) |
| IVA | 0 (0.0) |
| Frozen pathology records (n, %) | |
| Benign | 29 (12.8) |
| Borderline | 139 (61.5) |
| At least borderline | 46 (20.4) |
| Malignant | 12 (5.3) |
| Accuracy of frozen pathology (n, %) | 185 (81.9) |
| Presence of invasive implant (n, %) | 12 (3.3) |
| Surgery group (n, %) | |
| Conservative | 200 (54.9) |
| Radical | 164 (45.1) |
| Conservative surgery type (n, %) | |
| Unilateral cystectomy | 70 (35.0) |
| Bilateral cystectomy | 16 (8.0) |
| Cystectomy and contralateral ovarıan biopsy | 5 (2.5) |
| Unilateral salpıngo-oophorectomy (USO) | 103 (51.5) |
| USO and contralateral bıopsy | 6 (3.0) |
| Bilateral bıopsy | 0 (0.0) |
| Staging surgery (n, %) | |
| No | 217 (59.6) |
| Yes | |
| Complete | 92 (25.3) |
| Incomplete | 55 (15.1) |
| Appendectomy (n, %) | 194 (53.3) |
| Appendiceal involvement (n, %) | 33 (9.1) |
| Macroscopically abnormal appendicitis (n, %) | 12 (3.3) |
| Omentectomy (n, %) | 146 (40.1) |
| Hysterectomy (n, %) | 155 (42.6) |
| Median removed pelvic lymph nodes (n: range in numbers) | 17.9±9.0 (1-54) |
| Median removed para-aortic lymph nodes (n: range in numbers) | 19.4±11.9 (3-61) |
| Surgery type (n, %) | |
| Laparoscopy | 23 (6.3) |
| Laparotomy | 341 (93.7) |
| Received postoperative chemotherapy | 34 (9.3) |
| Recurrence (n, %) | 24 (6.6) |
| Treatment of recurrent tumor | |
| Surgery | 16 (4.4) |
| Chemotherapy | 2 (0.5) |
| Surgery + chemotherapy | 6 (1.6) |
| Disease-free survival (n: range in months) | 51.8±40.2 (12-216) |
| Overall survival (n: range in months) | 53.1±40.3 (12-216) |
| Duration of follow-up (n: range in months) | 53.1±40.3 (12-216) |

Patients with BOT other than the mucinous type or patients with any accompanying invasive cancer were excluded. Using the hospital databases, patient age, menopausal state, preoperative CA-125, and the results of preoperative ultrasound imaging were collected. The surgical technique, mean tumor diameter, lymph node status, and stage at diagnosis, if any, were reviewed. Chemotherapy after surgery, postoperative follow-up periods, and data related to disease recurrence were evaluated. If frozen sections (FS) were analyzed intraoperatively, FS results were reported intraoperatively as benign, borderline tumor, at least borderline tumor, or malignant tumor. Patients with incomplete data were excluded from the analysis.

Although the International Federation of Gynecology and Obstetrics (FIGO) ovarian staging classification was revised on January 1, 2014, we used the previous staging (2009 staging scheme) classification for consistency (11).

Surgical procedures were classified as radical or conservative. If both ovaries were removed, patients were included in the radical group. The conservative group included fertility-sparing surgery (such as unilateral salpingo-oophorectomy (USO), cystectomy, bilateral cystectomy, cystectomy with contralateral ovarian biopsy, and bilateral ovarian biopsy). For premenopausal women who desired pregnancy, conservative surgery was preferred. Moreover, patient operations were classified into three groups: complete staging, incomplete staging, or unstaged procedures. Staging was considered complete if peritoneal washing, peritoneal biopsies, appendectomy, and omentectomy were performed. If any of these four staging procedures was excluded, patients were considered incompletely staged. If only ovarian surgery (only ovarian cystectomy or oophorectomy) was performed, patients were considered unstaged (12).

After initial diagnosis, recurrence was defined as documentation of metastasis or a new tumor seen in one of the used imaging techniques. Progression-free survival (PFS) was defined as the time from the date of primary surgery to detection of recurrence or the latest observation. Overall survival (OS) was defined as the time from the date of primary surgery to death or the latest observation.

All statistical analyses were performed using MedCalc software (ver. 16.0 for Windows, MedCalc Software, Mariakerke, Belgium). 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 survival, presented as hazard ratios (HR). *p*-Value of <0.05 was considered statistically significant.

## Results

A total of 364 patients with mBOTs were identified during the study period. Clinicopathological characteristics of the patients are presented in Table I. Median age at diagnosis was 43.1 years (range=16-87 years). Nearly two out of three patients were premenopausal. Median tumor diameter was 113.25 mm (range=30-420 mm). In 226 patients (62%), frozen section was performed. The accuracy of frozen section was 81.9%. In 29 cases FS showed a benign disease=unterdiagnosed (12.83%) and in the other 12 cases a malignant disease=overdiagnosed (5.3%), which could not be confermed in the final pathological report.

A total of 26 patients received adjuvant chemotherapy (CT) after initial surgery. Eight for disease in early stages (stage IC or stage II) and eighteen for advanced stages (stages III and IV). Detailed surgical characteristics of the patients are demonstrated in Table I.

One hundred and sixty-four (45.1%) cases underwent radical excision procedures; the other 200 (54.9%) patients underwent conservative surgical procedures. Appendectomy was performed in 194 cases (53.3%). The number of patients with appendiceal involvement was 33 (9.1%). Appendiceal metastasis was seen in 5.7% (21) of patients in stage IIIA, 0.2% (1) of patients in stage IIIB, and 3.0% (11) of patients in stage IIIC. The rate of macroscopically abnormal appendix was 3.3% (12 patients). None of these patients had primary appendices carcinoma. The sensitivity of macroscopical abnormal appendix to predict appendical involvement was 36.4%, specificity 100%, positive predictive value 100% and negative predictive value 88.5%.

Omentectomy was performed in 146 patients (40.1%), and omental involvement was seen in only two of these cases. Implants were diagnosed in 12 patients (3.3%), and from those the appendix was affected in four cases (33%).

On univariate and multivariate analyses, FIGO stage (<IC or ≥IC), age (≥40 or <40), presence of an invasive implant, performance of radical surgery, lymphadenectomy, ovarian cystectomy, staging surgery, appendectomy, omentectomy, and receiving adjuvant chemotherapy were not independent prognostic factors for PFS or OS (Tables II and III).

Twenty-four patients (6.6%) experienced a recurrence. Thirteen (54.1%) of these patients were in the conservative surgery group and the remaining 11 (45.9%) were in the radical surgery group; this difference was not statistically significant ($p$=0.937). Furthermore, no statistically significant difference in recurrence was observed between complete, incomplete, and unstaged patients [(33.4%), (20.8%), and (45.8%), $p$=0.361]. Among patients with recurrence, two were managed with salvage chemotherapy, sixteen with only surgery, and six with chemotherapy after surgery.

The only predictors of recurrence were the FIGO/stage at first diagnosis and the presence of invasive implants. A total of 19 patients out of 328 patients with FIGO I relapsed (5.8%), whereas the rate of recurrence in patients with FIGO stage ≥ II was 13.9% (OR=2.6, $p$=0.13). The rate of invasive implants was significantly different between the two groups (recurrence *vs*. no recurrence) ((16.7 %) *vs*. (2.3 %), $p$<0.001). During the follow-up period, a total of 8 (2.2%) patients deceased from their disease (Table IV).

According to regression analysis, age (≥40 or <40), FIGO stage (<IC or ≥IC), performance of radical surgery, performance/nonperformance of surgical staging, performance of appendectomy, and first-line chemotherapy regimen were not independent risk factors for recurrence of mBOTs (Table V). Finally, in univariate and multivariate

Table II. *Results of univariate analyses of disease-free survival and overall survival of patients.*

| | Disease-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95%CI | *p*-Value | Hazard ratio | 95% CI | *p*-Value |
| Age (<40 yr *vs.* ≥40 yr) | 1.2 | 1.0-1.5 | 0.25 | 1.1 | 0.9-1.3 | 0.27 |
| Stage (<IC *vs.* ≥IC) | 1.0 | 0.8-1.2 | 0.71 | 0.8 | 0.7-1.0 | 0.64 |
| Radical surgery | 1.1 | 0.9-1.2 | 0.65 | 0.8 | 0.6-1.0 | 0.71 |
| Staging surgery | 1.0 | 0.9-1.1 | 0.29 | 1.0 | 0.9-1.1 | 0.29 |
| Ovarian cystectomy | 0.9 | 0.8-1.2 | 0.74 | 1.2 | 0.9-1.4 | 0.45 |
| Omentectomy | 1.0 | 0.8-1.2 | 0.57 | 1.0 | 0.9-1.1 | 0.40 |
| Invasive implant | 1.3 | 1.1-1.5 | 0.43 | 1.2 | 1.1-1.3 | 0.52 |
| Lymphadenectomy | 0.8 | 0.7-0.9 | 0.16 | 0.9 | 0.6-1.2 | 0.20 |
| Received adjuvant chemotherapy (stage ≥IC) | 1.0 | 0.9-1.1 | 0.30 | 1.0 | 0.8-1.2 | 0.72 |
| Appendectomy | 1.1 | 0.9-1.3 | 0.69 | 0.9 | 0.8-1.0 | 0.56 |

CI: Confidence interval.

Table III. *Results of multivariate analyses of disease-free survival and overall survival of patients.*

| | Disease-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95%CI | *p*-Value | Hazard ratio | 95%CI | *p*-Value |
| Age (<40 yr *vs.* ≥40 yr) | 1.2 | 0.9-1.5 | 0.06 | 1.2 | 0.9-1.5 | 0.08 |
| Stage (<IC *vs.* ≥IC) | 0.9 | 0.7-1.2 | 0.68 | 0.9 | 0.7-1.3 | 0.90 |
| Radical surgery | 1.0 | 0.7-1.3 | 0.85 | 0.9 | 0.7-1.2 | 0.93 |
| Staging surgery | 1.1 | 0.9-1.2 | 0.16 | 1.1 | 0.9-1.3 | 0.14 |
| Ovarian cystectomy | 1.0 | 0.9-1.1 | 0.61 | 1.1 | 0.8-1.2 | 0.23 |
| Omentectomy | 1.1 | 0.8-1.4 | 0.33 | 1.1 | 0.8-1.4 | 0.28 |
| Invasive ımplant | 1.4 | 1.2-1.6 | 0.31 | 1.3 | 1.1-1.5 | 0.17 |
| Lymphadenectomy | 0.7 | 0.6-0.9 | 0.06 | 0.7 | 0.5-1.0 | 0.08 |
| Received adjuvant chemotherapy (stage ≥IC) | 1.1 | 1.0-1.2 | 0.22 | 1.1 | 0.7-1.6 | 0.63 |
| Appendectomy | 1.0 | 0.8-1.2 | 0.64 | 1.0 | 0.8-1.2 | 0.71 |

CI: Confidence interval.

analysis, age (≥40 or <40), tumor size (>100 mm *vs.* ≤100 mm), menopausal status, and ovarian cystectomy were not independent risk factors for appendiceal involvement of mBOTs, but macroscopically abnormal appendix and FIGO stage (<IC or ≥IC) were independent risk factors for appendiceal involvement ($p$=0.032 and $p$=0.04) (Table VI).

## Discussion

BOTs are not a rare clinical entity; they constitute 10-20% of ovarian tumors (1), and 30-50% of BOTs are mucinous (3). In the literature, there are limited data evaluating only mBOTs. To the best of our knowledge this present study represents the largest series of cases, including only mBOTs, in the literature. The mean age of patients with BOTs was 43.1 years in our study. Moreover, 67.4% of patients were premenopausal. Our results support the knowledge of the occurrence of BOTs and mBOTs more frequently in young and premenopausal women (12-14).

Accurate intraoperative diagnosis is very important for mBOTs because it affects the preferred surgical approaches for treatment. However, mucinous histology was reported to be associated with low sensitivity in FS analysis in many studies (15, 16). Gultekin *et al*. evaluated 82 cases of BOT, 42.7 percent of whom had mucinous histology, and reported that the accuracy of frozen section was only 69% (17). The accuracy rate of our study is slightly higher than that of many previous studies. One reason may be that all our cases were operated in gynecological ongology centers.

In ROBOT-study (18) 96.2% of patients had stage I disease at the time of surgery for mBOT. Similarlly, in our study, FIGO I-disease was diagnosed too in a very high rate

Table IV. *Characteristics of patients based on recurrence.*

| | With recurrence (n:24) | Without recurrence (n:340) | *p*-Value | RR (95% CI) |
|---|---|---|---|---|
| Age (years)* | 39.4±14.4 | 43.4±15.5 | 0.225 | |
| Tumor size (mm)* | 79.2±43.4 | 114.9±73.3 | 0.112 | |
| Presence of invasive implant** | 4 (16.7) | 8 (2.3) | <0.001¥ | 8.3 (2.3-29.9) |
| Surgery type** | | | 0.188 | 0.9 (0.8-1.0) |
| Laparoscopy | 0(0.0) | 23 (6.7) | | |
| Laparotomy | 24 (100.0) | 317 (93.3) | | |
| Stage** | | | 0.123 | 1.9 (0.8-4.4) |
| <IC | 17 (70.9) | 283 (83.3) | | |
| ≥IC | 7 (29.1) | 57 (16.7) | | |
| Radical surgery** | | | 0.937 | 0.9 (0.4-2.1) |
| Yes | 11 (45.8) | 153 (45.3) | | |
| No | 13 (54.2) | 187 (54.70) | | |
| Staging surgery** | | | 0.361 | |
| Un-staged | 11 (45.8) | 206 (60.6) | | |
| Incomplete | 5 (20.8) | 50 (14.7) | | |
| Complete | 8 (33.4) | 84 (24.7) | | |
| Conservative surgery type (n, %)** | | | 0.825 | |
| Unilateral cystectomy | 6 (25.0) | 74 (21.7) | | |
| Bilateral cystectomy | 1 (4.1) | 15(4.4) | | |
| Cystectomy and contralateral ovarıan biopsy | 0 (0.0) | 5 (1.4) | | |
| Unilateral salpingo-oophorectomy (USO) | 8 (33.4) | 95 (27.9) | | |
| USO and contralateral biopsy | 1 (4.1) | 5 (1.4) | | |
| Bilateral biopsy | 0 (0.0) | 0 (0.0) | | |
| First-line chemotherapy regimen** | | | 0.202 | 2.0 (0.6-6.4) |
| Yes | 4 (16.7) | 30 (8.8) | | |
| No | 20 (83.3) | 310 (91.2) | | |
| Overall survival (months)* | 53.8±33.6 | 53.1±40.8 | 0.932 | |
| Disease-free survival (months)* | 36.1±27.3 | 52.9±40.8 | 0.049¥ | |

Data are expressed as *: mean±standard deviation; **: n (%); ¥: statistically significant.

(90%). Both results reveal the fact that the assessment of staging-procedures in small studies is very difficult, as we know already that the incidence of extra-gonadal mBOT (stages ≥FIGO II) is rare (4-10%). In other words, the effect of staging in extra-gonadal will be difficult to show, as the extra-gonadal disease is rare.

We found that lymphadenectomy in surgical staging does not affect survival or recurrence in mBOTs. Similarly, Fauvet *et al*. suggested that lymph node removal is not a part of surgical staging for mBOTs (19). Furthermore, Brown and Frumovitz reported in a review of 146 patients with mBOT that none had lymphatic metastases (20). Other studies claimed that lymph node involvement occurs in 21-29% of cases, leading to an upgrade in FIGO staging (21-24), but no change in PFS and OS (24-26).

Fertility-sparing surgery is even one other controversial issue in treatment of premenopausal mBOT. Koskas *et al*. stated that cystectomy alone is not recommended due to the high likelihood of mBOT developing into an invasive cancer. They attributed this to the presence of tumor cells in the margins, which can predict relapse after cystectomy (27). Other available data suggest that in general the rate of recurrence is higher after conservative management (10-20% *vs*. 5% for radical surgery) (1, 28-32). However, this higher recurrence rate did not result in a higher mortality rate in the so far largest series, the German ROBOT study (18). This is in line with our current study of mBOT, which shows that conservative surgery was not an independent prognostic factor for recurrence or PFS and OS.

It is very important to consider whether it is necessary to perform routine appendectomy in mBOT, as currently recommended in the National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer version-I 2016 (33). The literature is very confusing and controversial. Moreover, appendectomy may have surgical complications such as intraabdominal abscess, bleeding, and bowel perforation. The reviews by Kleppe *et al*. (3) and Cosyns *et al*. (34) both systematically evaluated 232 mBOT cases in which an appendectomy was performed and found only two (0.86%) appendiceal carcinomas. Since both were grossly

Table V. *Results of univariate and multivariate analyses of risk factors of patients with recurrence of mucinous borderline ovarian tumor.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard Ratio | 95%CI | *p*-Value | Hazard Ratio | 95%CI | *p*-Value |
| Age (<40 yr *vs.* ≥40 yr) | 1.1 | 0.9-1.4 | 0.224 | 1.1 | 0.9-1.4 | 0.173 |
| Stage (<IC *vs.* ≥IC) | 1.0 | 0.7-1.4 | 0.749 | 1.0 | 0.8-1.4 | 0.620 |
| Radical surgery | 0.9 | 0.7-1.1 | 0.315 | 0.9 | 0.7-1.2 | 0.823 |
| Staging surgery | 1.0 | 0.9-1.2 | 0.423 | 1.1 | 1.0-1.3 | 0.344 |
| Appendectomy | 0.9 | 0.7-1.2 | 0.907 | 1.0 | 0.8-1.2 | 0.816 |
| Cystectomy | 1.1 | 0.9-1.3 | 0.751 | 1.0 | 0.8-1.3 | 0.156 |
| First-line chemotherapy regimen | 1.1 | 0.8-1.6 | 0.373 | 1.2 | 0.8-1.9 | 0.293 |

CI: Confidence interval.

Table VI. *Results of univariate and multivariate analyses of risk factors of patients with appendiceal involvement of mucinous borderline ovarian tumor.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard Ratio | 95%CI | *p*-Value | Hazard Ratio | 95%CI | *p*-Value |
| Age (<40 yr *vs.* ≥40 yr) | 1.1 | 0.9-1.4 | 0.175 | 1.3 | 0.9-1.9 | 0.06 |
| Abnormal macroscopic appendicitis | 5.6 | 3.1-10.6 | 0.004¥ | 3.5 | 0.8-14.0 | 0.032¥ |
| Mean tumor diameter (≤100 mm *vs.* >100 mm) | 1.0 | 0.7-1.3 | 0.791 | 1.0 | 0.7-1.3 | 0.794 |
| Menopausal status | 1.0 | 0.8-1.3 | 0.563 | 0.9 | 0.6-1.3 | 0.650 |
| Stage (<IC *vs.* ≥IC) | 1.6 | 1.2-2.2 | 0.028¥ | 1.8 | 1.1-2.9 | 0.04¥ |
| Ovarian cystectomy | 0.9 | 0.7-1.2 | 0.69 | 1.0 | 0.8-1.2 | 0.81 |
| Invasive ımplant | 2.6 | 0.9-7.2 | 0.06 | 2.1 | 1.1-4.1 | 0.09 |

CI: Confidence interval; ¥: statistically significant.

abnormal at the time of surgery, they concluded that patients with mBOT with a normal appendiceal appearance should not undergo appendectomy.

Appendix was resected in 54% of cases in our current study. In 9.1% of resected appendices patients presented with appendiceal involvement. Only 36.4% of involved appendices schowed macroscopical abnormalities (12 out of 33 patients=low sensitivity of macroscopic abnormal appearance to predict the appendical involvement), therefore we could not conclude the same results and advise to omit the appendectomy from staging/procedures of mBOT, even when our data do not present any impact of appendectomy on PFS and OS.

Moreover, we found that routine omentectomy does not have any effect on PFS and OS in mBOT. This finding was similar to that of the study by Cömert *et al*. (13).

In the present study, surgery followed by sequential treatment with chemotherapy did not have different survival rates *versus* the absence of adjuvant chemotherapy in ≥IC FIGO stage mBOTs. This finding is similar to those of previous studies, and there were no additional benefits from postoperative adjuvant therapy for cases involving non-invasive or invasive implants (35, 36). One reason may be that mBOT generally does not show a high proliferation rate.

The rates of recurrence for mBOTs vary between 4.2 and 13% (27, 37). These data are similar to those of the present study (6.6%). Khunamornpong *et al*. reported that six patients (4.2%) developed a recurrent tumor, of whom only two underwent bilateral salpingo-oophorectomy (37). Moreover Koskas *et al*. found 13 recurrences (13%), of whom only three patients underwent bilateral salpingo-oophorectomy (27). However, according to our study, radical surgery does not protect against recurrence for mBOT. FIGO stage at the time of diagnosis was one of the strongest prognostic factors for recurrence in many studies (28, 38-39), While only 5% of patients initially diagnosed in FIGO stage I are confronted with relapse of the disease, patients with extended disease were faced with recurrence in up to 25% of cases. These data are very similar to our current findings, as we reported about 5.8% recurrence rate in FIGO I patients and about 13.9% recurrence rate in FIGO ≥II- Patients.

In the case of extragonadal recurrence, the best possible treatment is to perform cytoreductive surgery (18). Similar to this finding, in our series, most of the patients who experienced recurrence were treated with surgery without adding chemotherapy.

In our series, we found that, age (<40 or ≥40), the presence or absence of staging surgery, FIGO stage (≥IC *vs*. <IC), the presence of invasive implants, radical surgery, lymphadenectomy, omentectomy, appendectomy, cystectomy, and receiving adjuvant chemotherapy for stage ≥IC tumors were not independent prognostic factors for PFS and OS in mBOTs. These results are similar to those in the literature (27).

This study has many limitations. It was a retrospective analysis of patients from various institutions and countries. Furthermore, there were many different surgeons and surgical approaches. Additionally, histopathological evaluations of borderline ovarian tumors may vary depending on the experience of the institutions. On the other side, this study evaluated only mBOT patients and represents a very large multicenter series (including 364 patients) of cases with mBOTs. Moreover, lengthy follow-up increased the validity of the results and limited weaknesses.

In conclusion, the prognosis of patients with mBOT is excellent; moreover, patients who undergo conservative surgery do not have higher recurrence rates. Fertility-sparing surgery should be considered in the reproductive age group. Detailed surgical staging including lymphadenectomy, appendectomy, and omentectomy does not have an impact on survival rates.

## References


1 Suh-Burgmann E: Long-term outcomes following conservative surgery for borderline tumor of the ovary: A large population-based study. Gynecol Oncol *103(3)*: 841-847, 2006.

2 Hart WR and Norris HJ: Borderline and malignant mucinous tumors of the ovary. Histologic criteria and clinical behavior. Cancer *31(5)*: 1031-1045, 1973.

3 Kleppe M, Bruls J, Van Gorp T, Massuger L, Slangen BF, Van de Vijver KK, Kruse AJ and Kruitwagen RF: Mucinous borderline tumors of the ovary and the appendix: A retrospective study and overview of the literature. Gynecol Oncol *133(2)*: 155-158, 2014.

4 Timofeev J, Galgano MT, Stoler MH, Lachance JA, Modesitt SC and Jazaeri AA: Appendiceal pathology at the time of oophorectomy for ovarian neoplasm. Obstet Gynecol *116(6)*: 1348-1353, 2010.

5 Heerlein M, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, Hauptmann S and Sehouli J: Statement by the Kommission Ovar of the AGO: The new FIGO and WHO classifications of ovarian, fallopian tube and primary peritoneal cancer. Geburtsh Frauenheilk *75(10)*: 1021-1027, 2015.

6 Gershenson DM: Clinical management of potential tumours of low malignancy. Best Pract Res Clin Obstet Gynaecol *16(4)*: 513-527, 2002.

7 Feigenberg T, Covens A, Ghorab Z, Ismiil N, Dubé V, Saad RS, Khalifa MA and Nofech-Mozes S: Is routine appendectomy at the time of primary surgery for mucinous ovarian neoplasms beneficial? Int J Gynecol Cancer *23(7)*: 1205-1209, 2013.

8 Lin JE, Seo S, Kushner DM and Rose SL: The role of appendectomy for mucinous ovarian neoplasms. Am J Obstet Gynecol *208(1)*: 46.e 1-4, 2013.

9 Ozcan A, Töz E, Turan V, Sahin C, Kopuz A, Ata C and Sancı M: Should we remove the normal-looking appendix during operations for borderline mucinous ovarian neoplasms? A retrospective study of 129 cases. Int J Surg *18*: 99-103, 2015.

10 Cosyns S, Polyzos NP, Carprieaux M, Tournaye H and De Sutter P: The role of appendectomy as part of the treatment of a mucinous borderline ovarian tumor. Eur J Gynaecol Oncol *37(2)*: 167-170, 2016.

11 Benedet JL, Bender H, Jones 3rd H, Ngan HY and Pecorelli S: FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet *70(2)*: 209-262, 2000.

12 Gokcu M, Güngördük K, Asıcıoglu O, Cetinkaya N, Güngör T, Pakay G, Cüylan ZF, Toptas T, Özyurt R, Agaçayak E, Ozdemir A, Erol O, Turan A, Gülseren V, İcen MS, Şenol T, Güraslan H, Yücesoy B, Sahbaz A, Gungorduk O, Besimoğlu B, Pakay K, Temizkan O, Sancı M, Şimşek T, Meydanlı MM, Harma M, Yasar L, Boran B, Uysal AD and Karateke A: Borderline ovarian tumors: clinical characteristics, management, and outcomes – a multicenter study. J Ovar Res *9(1)*: 66, 2016.

13 Cömert DK, Üreyen I, Karalok A, Taşcı T, Türkmen O, Öcalan R, Turan T and Tulunay G: Mucinous borderline ovarian tumors: Analysis of 75 patients from a single center. J Turk Ger Gynecol Assoc *17(2)*: 96-100, 2016.

14 Messalli EM, Grauso F, Balbi G, Napolitano A, Seguino E and Torella M: Borderline ovarian tumors: features and controversial aspects. Eur J Obstet Gynecol Reprod Biol *167(1)*: 86-89, 2013.

15 Subbian A, Devi UK and Bafna UD: Accuracy rate of frozen section studies in ovarian cancers: a regional cancer institue experience. Indian J Cancer *50(4)*: 302-305, 2013.

16 Suprasert P, Khunamornpong S, Phusong A, Settakorn J and Siriangkul S: Accuracy of intra-operative frozen sections in the diagnosis of ovarian masses. Asian Pac J Cancer Prev *9(4)*: 737-740, 2008.

17 Gültekin E, Gültekin OE, Cingillioglu B, Sayhan S, Sanci M and Yıldırım Y: The value of frozen section evaluation in the management of borderline ovarian tumors. J Cancer Res Ther *22(3)*: 400-406, 2011.

18 du Bois A, Ewald-Riegler N , de Gregorio N, Reuss A, Mahner S, Fotopoulou C, Kommoss F, Schmalfeldt B, Hilpert F, Fehm T, Burges A, Meier W, Hillemanns P, Hanker L, Hasenburg A, Strauss HG, Hellriegel M, Wimberger P, Keyver-Paik MD, Baumann K, Canzler U, Wollschlaeger K, Forner D, Pfisterer J, Schröder W, Münstedt K, Richter B, Kommoss S and Hauptmann S; Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. Borderline tumours of the ovary: a cohort study of the Arbeitsgmeinscha Gynakologische Onkologie (AGO) Study Group. Eur J Cancer *49(8)*: 1905-1914, 2013.

19 Fauvet R, Boccara J, Dufournet C, David-Montefiore E, Poncelet C and Darai E: Restaging surgery for women with borderline ovarian tumors: results of a French multicenter study. Cancer *100(6)*: 1145-1151, 2004.

20 Brown J and Frumovitz M: Mucinous tumors of the ovary: current thoughts on diagnosis and management. Curr Oncol Rep *16(6)*: 389-397, 2014.
21 Kurman RJ, Seidman JD and Shih IM: Serous borderline tumours of the ovary. Histopathology *47(3)*: 310-315, 2005.
22 McKenney JK, Balzer BL and Longacre TA: Lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors): pathology, prognosis, and proposed classification. Am J Surg Pathol *30(5)*: 614-624, 2006.
23 Fadare O: Recent developments on the significance and pathogenesis of lymph node involvement in ovarian serous tumors of low malignant potential (borderline tumors). Int J Gynecol Cancer *19(1)*: 103-108, 2009.
24 Camatte S, Morice P, Thoury A, Fourchotte V, Pautier P, Lhomme C, Duvillard P and Castaigne D: Impact of surgical staging in patients with macroscopic 'stage I' ovarian borderline tumours: analysis of a continuous series of 101 cases. Eur J Cancer *40(12)*: 1842-1849, 2004.
25 Seidman JD and Kurman RJ: Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol *31(5)*: 539-557, 2000.
26 Desfeux P, Camatte S, Chatellier G, Blanc B, Querleu D and Lécuru F: Impact of surgical approach on the management of macroscopic early ovarian borderline tumors. Gynecol Oncol *98(3)*: 390-395, 2005.
27 Koskas M, Uzan C, Gouy S, Pautier P, Lhomme C, Haie-Meder C, Duvillard P and Morice P: Prognostic factors of a large retrospective series of mucinous borderline tumors of the ovary (excluding peritoneal pseudomyxoma). Ann Surg Oncol *18(1)*: 40-48, 2011.
28 Lenhard MS, Mitterer S, Kümper C, Stieber P, Mayr D, Ditsch N, Friese K and Burges A: Long-term follow-up after ovarian borderline tumor: relapse and survival in a large patient cohort. Eur J Obstet Gynecol Reprod Biol *145(2)*: 189-194, 2009.
29 Morice P, Camatte S, Rey A, Atallah D, Lhommé C, Pautier P, Pomel C, Coté JF, Haie-Meder C, Duvillard P and Castaigne D: Prognostic factors for patients with advanced stage serous borderline tumours of the ovary. Ann Oncol *14(4)*: 592-598, 2003.
30 Cadron I, Leunen K, Van Gorp T, Amant F, Neven P and Vergote I: Management of borderline ovarian neoplasms. J Clin Oncol *25(20)*: 2928-2937, 2007.
31 Morice P: Borderline tumours of the ovary and fertility. Eur J Cancer *42(2)*: 149-158, 2006.
32 Chan JK, Lin YG, Loizzi V, Ghobriel M, DiSaia PJ and Berman ML: Borderline ovarian tumors in reproductive-age women. Fertility-sparing surgery and outcome. J Reprod Med *48(10)*: 756-760, 2003.
33 Morgan RJ, Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Behbakht K, Chen LM, Copeland L, Crispens MA, DeRosa M, Dorigo O, Gershenson DM, Gray HJ, Hakam A, Havrilesky LJ, Johnston C, Lele S, Martin L, Matulonis UA, O'Malley DM, Penson RT, Percac-Lima S, Pineda M, Plaxe SC, Powell MA, Ratner E, Remmenga SW, Rose PG, Sabbatini P, Santoso JT, Werner TL, Burns J and Hughes M: Ovarian cancer, version 1.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw *14(9)*: 1134-1163, 2016.
34 Cosyns S, De Sutter P, Tournaye H and Polyzos NP: Necessity of appendectomy for mucinous borderline ovarian tumors. Systematic review. Arch Gynecol Obstet *294(6)*: 1283-1289, 2016.
35 Trope C, Kaern J, Vergote IB, Kristensen G and Abeler V: Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors. Gynecol Oncol *51(2)*: 236-243, 1993.
36 Vasconcelos I, Olschewski J, Braicu I and Sehouli J: A meta-analysis on the impact of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors with invasive implants. Oncologist *20(2)*: 151-158, 2015.
37 Khunamornpong S, Settakorn J, Sukpan K, Suprasert P and Siriaunkgul S: Mucinous tumor of low malignant potential ("borderline" or "atypical proliferative" tumor) of the ovary: a study of 171 cases with the assessment of intraepithelial carcinoma and microinvasion. Int J Gynecol Pathol *30(3)*: 218-230, 2011.
38 Tinelli R, Tinelli A, Tinelli FG, Cicinelli E and Malvasi A: Conservative surgery for borderline ovarian tumors: a review. Gynecol Oncol *100(1)*: 185-191, 2006.
39 Ren J, Peng Z and Yang K: A clinicopathologic multivariate analysis affecting recurrence of borderline ovarian tumors. Gynecol Oncol *110(2)*: 162-167, 2008.

*Received August 27, 2017*
*Revised September 18, 2017*
*Accepted September 19, 2017*