

## Effect of surgical staging on 539 patients with borderline ovarian tumors: A Turkish Gynecologic Oncology Group study

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### HIGHLIGHTS

- Extensiveness of surgical staging in patients with borderline ovarian tumors would not cause any differences on survival rates.
- Lymphadenectomy as part of surgical staging in BOT has no effect on survival.
- Appendectomy does not provide any advantage on survival of patients with BOT.

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### ABSTRACT

**Objective.** The objectives of this study were to examine demographic and clinicopathologic characteristics and to determine the effects of primary surgery, surgical staging and the extensiveness of staging.

**Methods.** In a retrospective Turkish multicenter study, 539 patients, from 14 institutions, with borderline ovarian tumors were investigated. Some of the demographic, clinical and surgical characteristics of the cases were evaluated. The effects of type of surgery, surgical staging; complete or incomplete staging on survival rates were calculated by using Kaplan–Meier method.

**Results.** The median age at diagnosis was 40 years (range 15–84) and 71.1% of patients were premenopausal. The most common histologic types were serous and mucinous. Majority of the staged cases were in Stage IA (73.5%). 242 patients underwent conservative surgery. Recurrence rates were significantly higher in conservative surgery group (8.3% vs. 3%). Of all patients in this study, 294 (54.5%) have undergone surgical staging procedures. Of the patients who underwent surgical staging, 228 (77.6%) had comprehensive staging including lymphadenectomy. Appendectomy was performed on 204 (37.8%) of the patients. The median follow-up time was 36 months (range 1–120 months). Five-year survival rate was 100% and median survival time was 120 months. Surgical staging, lymph node sampling or dissection and appendectomy didn't cause any difference on survival.

**Conclusion.** Comprehensive surgical staging, lymph node sampling or dissection and appendectomy are not beneficial in borderline ovarian tumors surgical management.

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## Introduction

Borderline ovarian tumors (BOTs) account for 10 to 15% of all ovarian tumors [1]. They appear in younger women, at an earlier stage and have better prognosis than malign ovarian tumors [2]. Although these tumors were defined approximately 80 years ago the optimal surgical management and staging of borderline ovarian tumors are still controversial. There are differences between the approaches of surgeons and institutions.

Although BOTs are staged according to the FIGO classification of ovarian cancer, there is no reliable evidence that comprehensive staging might be beneficial in these tumors. Furthermore, while some surgeons perform comprehensive surgical staging including lymphatic sampling or dissection similar to malign ovarian tumors, others prefer peritoneal washing, various biopsies, omentectomy and/or appendectomy excluding the lymph nodes [2,3]. Therefore, effects of surgical staging on BOTs have not been proven yet.

The aims of this Turkish multicenter retrospective study of women with BOT were to examine the demographic and clinical features and to determine the effects of types of primary surgeries, surgical staging and the extensiveness of staging on survival.

## Material and method

This retrospective study was planned by Turkish Society of Gynecologic Oncology Borderline Ovarian Tumors Study Group. This study was approved by one of the participating institutions' ethic committee (Ethic committee of Celal Bayar University). A data sheet with ninety-two variables including demographic, clinical, pathological, surgical characteristics, follow-up and survival status was sent to the members of the Turkish Society of Gynecologic Oncology to collect data about borderline ovarian tumors. Fourteen institutions – ten university hospitals and four training hospitals – answered and sent back their data. The data of 539 cases with borderline ovarian tumors were recruited.

If there was not enough data given by the institutions for some variables they were excluded from the study. These excluded variables were occupation, place of birth, family history, systemic diseases, causes of infertility, usage of fertility drugs, and metastatic lymph node count.

The included demographic characteristics were age, gravidity, menopausal status, obesity, smoking, infertility history, and tubal ligation history. Levels of CA 125, imaging techniques, morphological features of tumors in ultrasonography, and follow-up duration and last status (dead or alive) were evaluated under the clinical characteristics. Included surgical characteristics were frozen section diagnosis, type of primary surgery, whether or not they've undergone staging, type of staging, tumor stage and final pathologic results.

Staging was according to International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian carcinoma [4]. The follow-up interval was defined as the time between the patient's initial surgery to the last recorded inpatient or outpatient contact with the patient.

Primary surgical procedures were categorized as conservative or radical. If both ovaries of the patient were removed they were included in the radical group, if unilateral salpingo-oophorectomy (USO) or cystectomy was applied they were included in the conservative group. Patients were classified in two groups: the ones who have undergone surgical staging procedures and those who have not. Patients who have undergone surgical staging were divided into two groups based on the completeness of staging. If they've had peritoneal washing, omentum, and peritoneal biopsies as well as lymph node sampling or dissection were accepted as complete staging patients. If they've only had peritoneal washing, omentum or peritoneal biopsies without lymph node sampling or dissection were accepted as incomplete staging patients.

Data were categorized as numeric, nominal and ordinal. The Kolmogorov–Smirnov test was used to determine whether the data

**Table 1**

Demographic, clinicopathologic and surgical characteristics of patients with borderline ovarian tumors.

Age	
Median (n; range in years)	40 (15–84)
Menopausal status	
Pre-menopause	71.1%
Post menopause	28.9%
Median gravidity (n, range in numbers)	2 (0–21)
Nulligravidity	25.2%
Obesity	16.5%
Smoking (%)	20.1%
Infertility history	3.9%
Tubal ligation	1.7%
Histology	
Serous	61.6%
Mucinous	31.6%
Seromucinous	3.8%
Other (endometrioid, clear cell)	3.0%
Median CA-125 level (range in U/mL)	33.0 (2–2865)
Serous	197.9*
Mucinous	165.4
Median size (range in cm)	10 (2–35)
Initial stage (n, %)	
IA	294 (73.5)
IB	33 (8.3)
IC	40 [10]
IIA	8 [2]
IIC	2 (0.5)
IIIA	8 [2]
IIIB	4 [1]
IIIC	10 (2.5)
IVA	1 (0.3)
Surgery (n, %)	
Conservative	242 (44.9)
Radical	297 (55.1)
Conservative surgery (n, %)	
USO	166 (68.6)
Cystectomy	72 (29.8)
Biopsy only	4 (1.7)
Staging surgery (n, %)	
None	245 (45.5)
Yes	294 (54.5)
Complete staging	228 (77.6)
Incomplete staging	66 (22.4)
Appendectomy (n, %)	
None	335 (62.2)
Yes	204 (37.8)
Serous	113 (57.1)
Mucinous	73 (36.9)
Median removed LN (n, range in numbers)	25.5 (1–135)
Median follow-up (range in months)	
Recurrence (n, %)	36 (1–120)
Yes	29 (5.4)
No	508 (94.6)
Recurrence (n, %)	
Conservative (n = 240)	20 (8.3)**
Radical (n = 297)	9 [3]
Last follow-up status (n, %)	
DOD	6 (1.2)
NED	486 (98.8)

LN; lymph node; DOD; death of disease, NED; no evidence of disease.

\*  $p = 0.007$ .

\*\*  $p = 0.011$ .

had normal or non-normal distributions. If data showed non-normal distributions, non-parametric tests such as Mann–Whitney U test were used. Frequency distributions were compared using the Chi-squared test. Overall survival (OS) was defined as the time, in months, from the date of surgery to the date of death, last follow-up, or censoring. The Kaplan–Meier method was used to estimate the impact of staging on survival of patients and groups were compared using the log-rank test. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL). Statistical significance was as  $p < 0.05$ .

## Results

A total of 539 cases with borderline ovarian tumor from 14 institutions were evaluated in this retrospective study. The demographic and clinicopathologic characteristics are presented in Table 1. The median age at diagnosis was 40 years (range 15–84) and 71.1% of patients were premenopausal. The median gravidity was 2 (range 0–21) and 25.2% were nulligravida. Of all the patients, 16.5% were obese, 20.1% were smokers and 3.9% were infertile. Tubal ligation percentage was 1.7. Among 539 patients with BOTs, the most common histologic type was serous (61.6%) then mucinous (31.6%), seromucinous (3.8%) and other types (endometrioid and clear cell histology) (3.0%). The median CA 125 levels were 33 Unit/mL (range 2–2865). The levels of CA 125 were significantly higher in serous types compared to mucinous (197.9 Units/mL vs. 165.4 Units/mL, respectively,  $p = 0.007$ ). The median size of BOTs was 10 cm (range 2–35). A total of 400 cases have been staged according to FIGO. Most of the staged cases were Stage IA (73.5%). The median follow-up time was 36 months (range 1–120 months). The last follow-up statuses of 47 patients were unknown. There was recurrence in 29 patients; 20 of these patients were in the conservative surgery group and the remaining 9 patients were in the radical group. Patients who underwent conservative surgery had significantly higher recurrence rate than radical surgery patients ( $p = 0.011$ ) (Table 1). Patients with recurrence were managed only surgically. Of the known last follow-up statuses 6 (1.2%) died from the disease while 486 (98.8%) had no evidence of the disease.

Two hundred and ninety-seven (55.1%) cases underwent radical excision procedures (bilateral oophorectomy), while 242 (44.9%) patients underwent conservative surgical procedures (unilateral salpingo-oophorectomy, cystectomy or only biopsy). In the conservative surgery group, 166 (68.6%) cases had USO, 72 (29.8%) had cystectomy and 4 (1.7%) had ovarian biopsy. Of all patients in this study, 294 (54.5%) have undergone surgical staging procedures. Of the patients who underwent surgical staging, 228 (77.6%) had comprehensive staging; including peritoneal washing, omentectomy or omental biopsy, peritoneal biopsy and pelvic and/or para-aortic lymph node sampling or dissection, while 66 (22.4%) had incomplete staging including peritoneal washing, omental and/or peritoneal biopsy. If the patients had undergone only appendectomy, we did not include them in the staged group. Appendectomy was performed on 204 (37.8%) of the patients and was mostly performed on patients with serous borderline ovarian tumors when compared to mucinous histology (57.1% vs. 36.9%, respectively). In the completely staged group, median removed the pelvic and/or para-aortic lymph node counts were 25.5 (range 1–135) (Table 1).

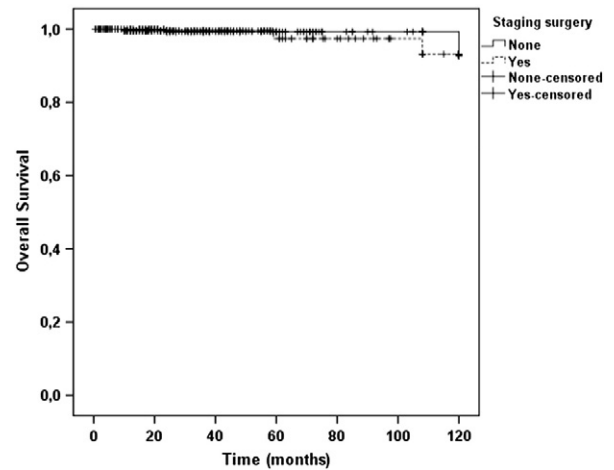


Fig. 2. Survival rates of surgically staged patients and not surgically staged patients.

Of the 539 patients with borderline tumors, 327 (60.7%) had intraoperative histologic diagnosis. We found that the sensitivity of frozen sections was 84.1% for the diagnosis of borderline tumors. The predictive value of frozen section was 96.3% for borderline tumors.

Five-year survival rate of patients with borderline ovarian tumors was 100% and median survival rate was 120 months. In this study, we could not find any differences between patients who underwent conservative surgery and patients who underwent radical surgery ( $p = 0.135$ ) (Fig. 1). There were no differences on survival rates between surgically staged patients and not surgically staged patients ( $p = 0.690$ ) (Fig. 2). Survival rates were also similar in completely and incompletely staged patients ( $p = 0.888$ ) (Fig. 3). When the impact of lymph node sampling or dissection on survival was assessed, it was observed that lymph node removal made no difference on survival ( $p = 0.861$ ) (Fig. 4). In borderline ovarian tumors, adding appendectomy to the surgical procedures did not affect survival ( $p = 0.218$ ) (Fig. 5).

## Discussion

Even though a lot about the clinical behavior and prognosis of borderline ovarian tumors are well known, there is still no consensus about the surgical management of these cases. In this study, we as Turkish Gynecologic Oncology Society investigated patients from various institutes with borderline ovarian tumors, their demographic,

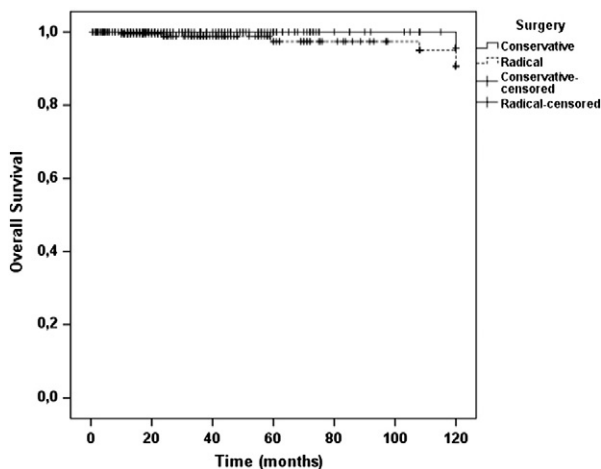


Fig. 1. Survival of patients who underwent conservative or radical surgery.

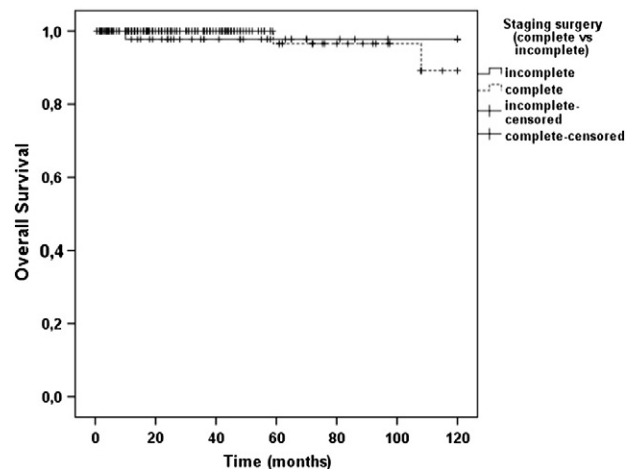


Fig. 3. Survival of completely and incompletely staged patients.

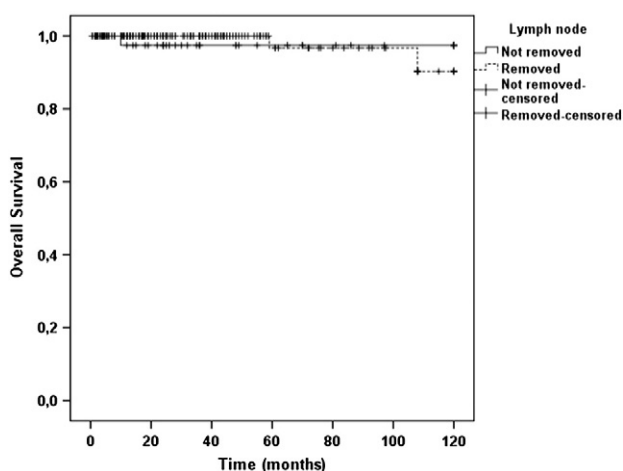


Fig. 4. Survival curve according to lymph node sampling or dissection, yes/no.

clinicopathologic characteristics and especially surgical management results. To our knowledge, this study represents one of the largest series of cases with borderline ovarian tumors. Similar to other studies, these cases were mostly in the premenopausal as well, and the median age was 40 [5–7]. Although it was suggested that nulliparity and smoking are risk factors [8,9], in this study nulliparity and smoking rates were lower. This might be related with socio-economic and cultural differences in the study population.

In accordance with other studies [6,10–12], the most common histology types were serous and mucinous in present study. Serous histology was more common in our study with 61.6%. In Song T et al.'s study the main histologic type was mucinous. They suggested that in Western countries serous histologic type is more common and in Eastern countries mucinous histologic type is more frequent [13].

It is well known that another important point in the management of BOTs is the accurate intraoperative diagnosis. In present study, intraoperative diagnosis of borderline ovarian tumors was satisfactory, sensitivity and predictive values were 84.1% and 96.3%, respectively. The accuracy of frozen section diagnosis of borderline ovarian tumors has been studied in multiple retrospective studies and accuracy rates have varied widely from 45 to 87% [13–16]. It has been shown that tumor size is an important factor in frozen section diagnosis [13,17]. Tumor size >15 cm may cause misdiagnosis. Because the median tumor size is 10 cm, frozen section sensitivity is higher in this study.

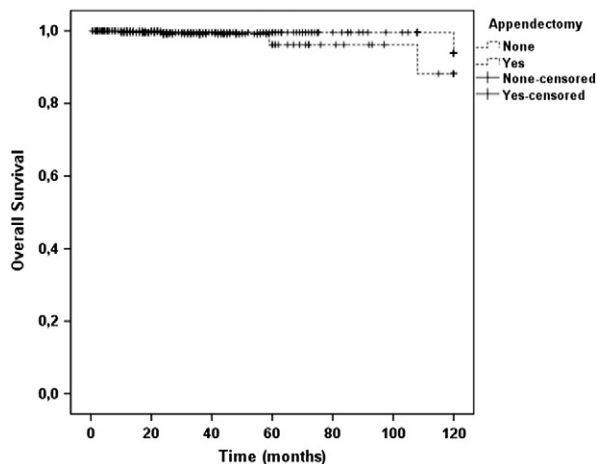


Fig. 5. Survival according to appendectomy, yes/no.

In the management of borderline ovarian tumors, the most important and controversial issue is how to approach patients surgically. Considering fertility-sparing or conservative surgery for young women who desire preservation of fertility is the general approach. However, these patients have higher recurrence rates compared to the radical surgery group like what we showed in our study (8.3% vs. 3%). Similarly, Boran et al.'s study shows that the patients who underwent radical surgery have 0.0% recurrence whereas the patients who underwent fertility-sparing surgery have 6.5% recurrence, respectively [5]. Ren J et al.'s showed that a conservative surgical procedure is an independent predictive factor for recurrence [10]. In accordance with our results, Suh-Burgmann E found 11% recurrence rate after conservative surgery; half of these patients were treated with repeat surgeries [18]. Although recurrence rates in our patients with conservative surgery were higher than those with radical surgery, there were no differences on survival rates (Fig. 1).

Even though borderline ovarian tumors have different clinical characteristics, they are still staged and managed as ovarian cancer. In present study, half of our patients were staged and the remaining was unstaged (54.5% vs. 45.5%, respectively), and the majority of the staged cases were completely staged (including lymph node sampling or dissection) like ovarian cancer. This study has one of the largest groups with 294 patients who underwent surgical staging and of these patients 228 had complete staging including lymph node sampling or dissection. For instance, in a French multicenter study only 37 patients underwent complete surgical staging procedure including peritoneal washing, multiple biopsy, omentectomy, and, for women with mucinous borderline tumors, appendectomy. Only 3 patients underwent lymphadenectomy [3]. In Suh-Burgmann's study, additional staging procedures beyond peritoneal washings were not done to 69% of patients. Fifteen patients (8%) had complete staging with omental biopsy, lymph node biopsies and appendectomy [18]. Even though more cases had surgical staging in our study when compared to other studies, there were no differences between the survival rates of staged and unstaged patients (Fig. 2). When staged group was evaluated according to its completeness, no differences were found between completely and incompletely staged patients as well (Fig. 3). In accordance with our results, Desfeux P. et al. showed that the extensiveness of surgical staging didn't cause any differences on survival in their study [19]. Also, Winter WE et al. found that survival rates were not different between staged and unstaged patients with BOTs [20].

The need of complete surgical staging including lymph node sampling or dissection is controversial. Although some authors accept that lymph node removal is not a part of surgical staging for borderline ovarian tumors [3,21], this procedure is still performed on some of the patients with BOTs [6,10,18,19]. In this study we showed that lymph node removal in surgical staging does not affect survival (Fig. 4). In borderline ovarian tumors the low prognostic utility of lymph node sampling was illustrated in some studies [22–24]. Camatte S et al. suggested that routine lymphadenectomy should not be performed in patients with early-stage borderline ovarian tumors [24]. These results are in accordance with our outcomes. Another procedure on the surgical staging of BOTs is appendectomy. Adding appendectomy to surgical staging procedures is recommended for mucinous tumors particularly [2]. In our study approximately 40% of cases had appendectomy, most of which was serous histology. However, appendectomy doesn't have an impact on survival (Fig. 5).

This study has some important limitations. It was a retrospective analysis of patients from various institutions. There were many different surgical approaches, which may have caused bias. Histopathologic evaluations of borderline ovarian tumors may vary depending on the experience of the institutions. Therefore, lack of central pathologic analysis is another important drawback of this study.

In conclusion, this retrospective study with a large pool of patients shows that borderline ovarian tumors have excellent survival rates.

Although patients with conservative surgery have higher recurrence, survival time is not shortened. Extensiveness of surgical staging including lymph node sampling or dissection and appendectomy does not cause any differences on survival rates. Even though this study indicates that comprehensive surgical staging should not be performed on BOT patients; prospective randomized studies are necessary to reach clear conclusion.

#### Conflict of interest

The authors declare that there are no conflicts of interest.

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