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Gynecological Cancer

Retrospective Analysis of Factors Affecting Recurrence in Borderline Ovarian Tumors

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Abstract

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Background Borderline ovarian tumors (BOTs) are an intermediate form of neoplasia, between benign and malignant. The aim of this retrospective analysis is to evaluate the clinicopathological characteristic profile of BOTs and to determine the predictors of recurrence in BOTs.

Materials and Methods A retrospective review of all patients diagnosed, treated, and followed up for BOTs between 2010 and 2017 at Amrita Institute of Medical Sciences, Kerala, India, was conducted. Clinicopathological details and details of management, outcome, and survival were retrieved, and data were analyzed descriptively and for survival.

Results A total of 103 patients were identified. During the median follow-up of 46.0 months, 15 (14.6%) patients developed recurrent disease, 6 (5.82%) had recurrence with progression to invasive carcinoma, and 9 had recurrent disease with borderline or benign histology. Mucinous tumors were found to have more recurrences than serous BOT (17.8 vs. 12.3%). Disease-related deaths (5/103 [4.9%]) were observed only in patients with progression to invasive carcinoma. Univariate analysis indicated that staging surgery was the most important prognostic factor that affected the disease-free survival ([DFS] 103 vs. 97 vs. 71 months, respectively, for complete staging vs. fertility-preserving staging vs. conservative surgery; $p < 0.05$).

Conclusions Conservative surgery was associated with a higher risk of recurrence. Fertility-preserving staging surgery is an acceptable option in younger patients. The overall survival is not affected by the mode of surgery.

Keywords

- borderline ovarian tumors
- implants
- low malignant potential
- predictors
- progression to invasive carcinoma
- recurrence
- reproductive outcome

Introduction

Borderline ovarian tumors (BOTs), first described by Taylor in 1929, qualified as tumors of low malignant potential, have a better prognosis with excellent survival in contrast to ovarian cancers.[1] They comprise a subset of all epithelial ovarian neoplasms, accounting for 10 to 20%, and are characterized by atypical cellular proliferation and nuclear atypia without destructive stromal invasion.[1,2]

The epidemiological shift that makes them distinct is the presentation in younger women at an earlier stage.[3,4] Choosing the optimum treatment for these patients can be a challenge as they will be desirous of fertility.

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Long-term surveillance is recommended for borderline neoplasms as there can be late recurrences even after 10 years, and there is a rare chance of malignant transformation.[5,6] The 5 and 10-year survival rates for stage I, II, and III disease are 99 and 97%, 98 and 90%, and 96 and 88%, respectively.[5,6] Recurrences in patients with BOTs were subclassified into two types: (1) borderline-type recurrence and (2) invasive-type recurrence (progression to invasive carcinoma).[7] Factors such as the presence of micropapillary patterns and stromal microinvasion in serous BOTs (SBOTs), presence of intraepithelial carcinoma in mucinous lesions, and use of cystectomy in mucinous BOTs are considered controversial, and their effect on recurrence is yet to be established. Besides, the International Federation of Gynecology and Obstetrics (FIGO) higher stage, incomplete surgical staging, presence of residual tumor, and fertility preservation strategy were recently confirmed to be independent prognostic factors for recurrence of disease in a cohort study on BOT.[8]

Herein, we present the results of a retrospective study conducted to evaluate the clinicopathological characteristics and high-risk factors affecting the relapse in patients with BOTs.

Methods

This retrospective study was conducted at Amrita Institute of Medical Sciences, Kochi, South India, after approval by the Institutional Scientific Committee. All consecutive patients with pathologically confirmed BOTs who were treated at the institution between January 2010 and December 2017 were included in the study. Data were obtained from electronic medical records. Patients who did not receive primary treatment or did not come for follow-up for at least 6 months were excluded from the analysis. Demographics, preoperative imaging and clinicopathological finding, tumor markers, and treatment details were collected.

Surgical approach was classified as open, laparoscopic, or robotic. The surgical treatment was also divided for evaluation as (1) conservative (any patient with bilateral cystectomy, unilateral salpingo-oophorectomy with contralateral cystectomy for bilateral ovarian neoplasm, or unilateral cystectomy), (2) staging surgery (bilateral salpingo-oophorectomy with or without hysterectomy, with omentectomy, peritoneal washing cytology, peritoneal biopsies, and appendectomy [in mucinous tumor types]), and (3) fertility-sparing surgery (defined as conservation of the uterus and at least a portion of one ovary). The completeness of the surgical staging was evaluated according to the FIGO guidelines. For patients with fertility preservation, surgical staging was considered comprehensive when, apart from the reproductive organs, the same surgical steps as described for staging surgery were performed.

The current World Health Organization criteria were strictly adhered to for the diagnosis of BOTs by the pathologists. Extraovarian implants were divided histologically into noninvasive and invasive implants characterized by the absence or presence of destructive stromal invasion into the underlying tissue, respectively.

After completion of the primary treatment, during the first 2 years, patients were examined every 3 months, every 6 months during the next 3 years, and thereafter yearly. Posttreatment surveillance included physical examination, assessment of tumor markers, and imaging studies. Recurrence was defined as the detection of the same tumor cell histology after an apparently complete surgical resection.

Overall survival (OS) was calculated from the date of surgery to the date of disease-related death or last contact. Progression-free survival was defined as the date of surgery to the date of recurrence.

The whole study group was compared (1) based on histology of borderline neoplasm, (2) conservative surgery versus comprehensive staging surgery versus fertility-sparing surgery, (3) tumor recurrence rate, and (4) progression to invasive carcinoma rate, and thereby mortality rates were analyzed. The outcomes were correlated with age, FIGO stage, surgical approach (open or minimally invasive surgery), surgical radicality, operating surgeon (nononcosurgeon vs. oncosurgeon), type of peritoneal implants (invasive versus noninvasive), and histological type. Reproductive outcome was also assessed separately.

Statistical Analysis

Collected data were analyzed by the statistical software IBM SPSS statistics (version 20.0, IBM Corp., Armonk, New York, United States), and qualitative and quantitative data were analyzed using the chi-square test and Student's *t*-test, respectively. Progression-free survival and OS were analyzed using the Kaplan–Meier method, and time-to-event outcome was compared with log-rank test; $p < 0.05$ was considered statistically significant. For association of categorical variables, the chi-square test was used. Survival analysis with the recurrence pattern was performed using the Kaplan–Meier analysis approach with log-rank test to look into their significance.

Results

A total of 1,060 patients presented with epithelial ovarian tumor between January 2010 and June 2017. Of the, 110 (10.4%) patients were identified with BOTs. Of the 110 patients, 7 did not satisfy the eligibility criteria and were excluded from the study. A total of 103 patients were included in the study group, having a median follow-up of 46 months (range: 23–130 months). ►Table 1 presents the demographic details of the study cohort. The median age of the study population was 41 years, with 43.7% < 40 years of age. The most common presentation was mass per abdomen in 46% followed by pain abdomen in 34% of the patients, and 20% were asymptomatic and detected incidentally on ultrasonography. The young patients who were desirous of fertility were 43.7%. Around 17.5% of the women had ascites on presentation. Tumor was unilateral in 87 (84.5%) patients, whereas it was bilateral in the remaining 16 (15.5%) patients. Cancer antigen 125 (CA-125) was elevated beyond 35 IU/mL in 26% of the patients, and of them, 18% had a value > 100 IU/mL. Carcinoembryonic antigen was elevated in 7.8% of the patients among all mucinous borderline neoplasm. The histopathological features are given in ►Table 2.

Among patients managed surgically, open approach (75.7%) was preferred over laparoscopy and robotic approaches, accounting to 21.4 and 2.9%, respectively. Almost 31.1% had conservative surgery such as unilateral or bilateral cystectomy, 51.5% had complete peritoneal staging surgery, and 17.5% had fertility-preserving surgery (►Table 3). Around 41.7% of the patients were operated by nononcosurgeons and referred to our hospital, 43.7% were operated by combined nononcosurgeon and oncosurgeon, and 14.6% were operated by an oncosurgeon. All tumors were staged as per the FIGO staging criteria 2014.

Of the 103 patients, 98 are alive after median of 46 months of follow-up. Fifteen (14.6%) recurrences were recorded. Almost 5.82% had malignant transformation at recurrence. Six patients had died, of which five (4.9%) deaths were specific to disease (had malignant transformation at recurrence). Looking at the relation of age with recurrences, nine (20%) patients who experienced recurrences were <40 years of age (p = 0.16). Three of six malignant transformations were in patients above the age of 40 years.

Looking at the relationship with stage, 9 (11.4%) recurrences were in stage IA, 5 (31.2%) in stage IC, and 25% in stage IIB1 disease. In 15 of 103 recurrences, nine were in stage I and five women who progressed to malignancy were from stage I. Younger patients with recurrences were predominantly in the early stage I (88.3% in stage I). Looking at the relationship with histology, mucinous histology was significant for recurrences. Malignant histology was also higher in the mucinous variety. Recurrences in serous papillary histology were 7/57 (12.3%) and that in mucinous variety were 8/45 (17.8%), of which 4 were mucinous endocervical and 4 mucinous intestinal.

The type of surgery performed was found to be a significant factor affecting the recurrences (►Table 3). Completing the surgical staging reduced the chance of recurrences in BOT. Focusing on six patients who underwent malignant transformation, observation was made that all underwent initially conservative surgery. The type of surgery or surgeon did not seem to affect the number of recurrences in BOT.

Extraovarian implants were found in 10.67% (11/103) of the patients. Seven patients had invasive implants and four patients had noninvasive implants. Only one patient had recurrence among patients with invasive implants, and she was alive till the end of the study period. Among all patients recurred with invasive implants, none progressed to malignancy. Five patients with invasive implants received six cycles of adjuvant chemotherapy. Difference in survival for extraovarian invasive versus noninvasive implants was not statistically significant (95 vs. 102 months, respectively; p = 0.53).

Thirteen patients conceived during the follow-up period, of which one had a miscarriage.

Looking at the relationship of recurrences with histology, 17.8% (8/45) had a mucinous BOT, 12.3% (7/57) were serous micropapillary. Of the five cancer-related deaths, four were in women with mucinous tumors (4/45–8.9%) and one serous papillary with microinvasion (1/57–1.8%), who succumbed to death. In our study, micropapillary pattern showed no significance in recurrence. Outcome in women with mucinous tumors looks clinically worse compared with serous tumors, but the difference was not statistically significant (p = 0.676).

Complete staging surgery was found to have a better DFS outcome in comparison with fertility-sparing surgery and conservative surgery (103 vs. 97 vs. 71 months, respectively) (►Fig. 1). No difference was found in the OS with 113 versus 121 versus 125 months for complete staging

Table 1 Demographic details of the study population

Patient characteristics	n = 103
Median (years) (range)	41 (14–80)
Parity, n (%)	
Nulliparous	35 (34)
Muciparous	68 (66)
Evaluation for infertility	13 (12.6)
Menopausal state, n (%)	
Premenopausal	64 (64)
Postmenopausal	36 (36)
Stage, n (%)	
IA	72 (69.9)
IB	7 (6.8)
IC	16 (15.5)
II	4 (3.9)
IIIB	1 (1)
IIIC	3 (2.9)

Table 2 Histopathological classification in the study population (n = 103)

	Serous	Mucinous	Endometrioid
Number of cases (n = 103), n (%)	57 (55.3)	45 (43.7)	1 (1)
Median age	38	44	47
Bilateral, n (%)	14 (29.5)	2 (4.5)	0
Invasive implant	3	4	0
Micropapillary	8	0	0
Microinvasion	6	7	0
Intraepithelial carcinoma	2	4	0

Table 3 Clinicopathological characteristics in relation to borderline ovarian tumor recurrences

Clinicopathological characteristics	Total cases (*n*)	Recurrence (%)	*p*-Value
Age (years)			
<40	45	9 (20)	0.168
>40	58	6 (10.3)	
Stage			
IA, B	79	9 (11.4)	0.154
IC	16	5 (31.2)	
IIB	4	1 (25)	
III above	4	0	
Histology			
Serous	57	7 (12.3)	0.676
Mucinous	45	8 (17.8)	
Endometrioid	1	0	
Operating surgeon			
Nononcosurgeon	44	7 (15.9)	0.783
Oncosurgeon	59	8 (13.6)	
Surgery approach			
Open	77	9 (11.7)	0.099
MIS	26	6 (23.122)	
Surgical intervention			
Conservative surgery	32	9 (28.1)	0.007
Staging surgery	53	3 (5.7)	
Fertility-preserving surgery	18	3 (16.7)	

Abbreviation: MIS, minimally invasive surgery.

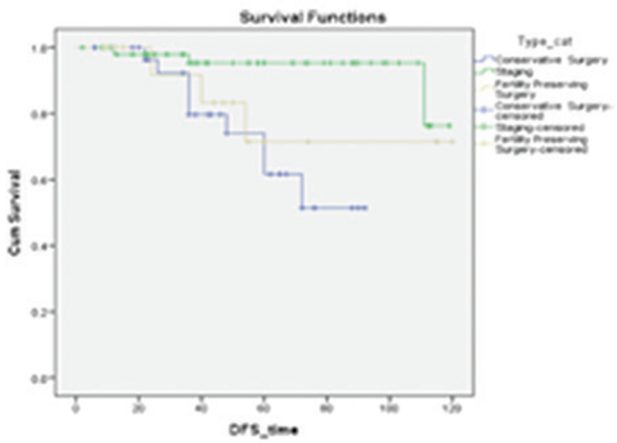

Fig. 1 Kaplan–Meier plot: survival probability by the type of surgery with conservative surgery (c), comprehensive staging (s), and fertility-sparing surgery (sf) statistically significant.

surgery, fertility-sparing surgery, and conservative surgery, respectively (►Fig. 2).

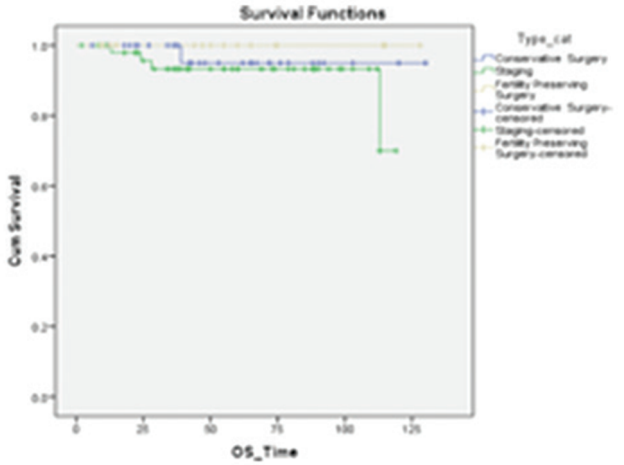

Fig. 2 Kaplan–Meier plot: overall survival of the surgical intervention group.

Table 4 Published studies comparing recurrence percentage with other study analysis

Recurrence	Total, *n* (%)
Walter H Gotieb et al (1998)	82 (4.87)
Zanetta G et al (2001)	339 (12.3)
Lazarou A et al (2014)	151 (16.8)
Present study	103 (14.6)

Discussion

BOT is an intermediate form of neoplasia, between benign and malignant. In our retrospective analysis of the clinicopathological characteristics and predictors of recurrence in BOT, staging surgery was seen as the single most important factor affecting recurrence.

It was observed that no patient with borderline type of recurrence died of the disease, and disease-related death was observed only in patients with progression to invasive carcinoma similar to other studies.[7] Identification of patients with high-risk factors (i.e., advanced stage, old age, micropapillary and microinvasion, mucinous histology, ascites, type of surgical approach, adequate staging or fertility-preserving surgery, and residual disease) is essential for offering more selective therapeutic strategies or monitoring to prevent progression to invasive carcinoma.

►Table 4 compares our recurrences to published studies. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study reveals that recurrence was significantly more frequent in patients <40 years, and relapse was usually in residual ovarian tissue.[6] In our analysis, there was no difference in survival by age.[7] In this analysis, advanced FIGO stage was not an independent risk factor. Some studies[8,9] concluded that advanced FIGO stage was a significant risk factor for disease-specific mortality as well as for recurrence and progression to invasive carcinoma. More recurrences were seen in stage I, and all five deaths (cancer related) that had progressed to invasive and lethal consequence were in FIGO stage

I A/C. Contrary to our observations, Camatte et al[10] reported that the absence of a staging procedure in patients with an "apparent stage I" BOT does not modify survival. Similar to our observation, clinical audit at the University of Cape Town found that 5.6% of early-stage disease had died of cancer, similar to our study.[11]

In our study, the risk of progression to invasive carcinoma was 5.8%. This rate was similar to three previous studies.[8,12,13] Morice et al[14] reported a 2 to 3% progression rate in their study. Song et al[7] reported that SBOTs seemed to be more prone to progression to invasive carcinoma (5.5 vs 2%; $p = 0.104$), the progression rate was 3.3%, and the independent risk factors for progression were advanced FIGO stage, age 65 years or older, and the presence of microinvasion also related to OS.[7] Contrary to that, in our study, mucinous histology (5/6 in 103 women) was more prone to malignant transformation, whereas the histological type did not significantly differ between the mucinous and serous histologies for recurrences. Koskas et al[15] report that the 10-year cumulative risk of recurrence in the form of invasive carcinoma was 13% with mucinous BOT and concluded that, unlike SBOT, mucinous BOT does not appear to be such a "safe" disease.

In terms of histology, 43.7% had a mucinous BOT and 55.3% were serous papillary; this differs from most international data where SBOT occurred more frequently.[16] Of the five deaths, all five were in women with mucinous tumors.

To preserve fertility potential, Morice et al[14] conducted a review looking at the results of epithelial malignant and BOTs and proposed that conservative management could be performed in patients with BOT[16] and also concluded that this management would not affect survival in these patients. There is a place for conservative management in younger women who have not completed their childbearing,[17] and it appears safe to carry out conservative surgery as long as they do not have an invasive implant as well. Our study also shows that fertility-preserving staging is an acceptable option in women desirous of future pregnancy. All cancer-related deaths were recorded in 103 BOT-affected women who underwent conservative surgery without adequate staging. The patients who underwent complete staging surgery had the best DFS, whereas OS did not seem to differ in conservative versus fertility-sparing versus complete staging groups. du Bois et al showed that higher stage, incomplete staging, tumor residuals, and organ preservation were all independent prognostic factors for disease recurrence.[5]

Adjuvant chemotherapy is currently not believed to play a role in the treatment of BOTs. Of 103 women, five with invasive implants received six cycles of adjuvant chemotherapy in the form of platinum-based regimens. Chemotherapy was mainly indicated in patients with advanced-stage disease.[18]

Our study is one of the few studies to determine the predictors for recurrence of BOTs.[18] Our observation with BOT is that they have a good OS. We looked into several factors that were reported to affect the outcome but found that the type of surgery was the only factor that significantly influenced the chance of having a recurrence. Fertility-sparing surgery is an acceptable option for a woman who is desirous of pregnancy.

Nevertheless, the results have to be cautiously interpreted as this is a single-institution retrospective study. Future prospective multicentric studies are needed, as most of the current studies on BOT have been conducted retrospectively.

BOTs may have a very long natural history and can recur up to 20 years after initial diagnosis; therefore, long-term evaluation is required to elucidate better the natural history. Follow-up should also occur for a long time as relapses may occur 15 years after surgery, and in our analysis, one recurrence was after 11 years, and the same patient succumbed to death as it was a disseminated disease. Close monitoring is advised for women treated with conservative surgery because of the high rate of relapse. Fertility-sparing approach can be done for younger patients after thorough consultation.

Conclusions

Complete staging surgery is an important prognostic factor for DFS in BOT. However, fertility-sparing surgery is also an acceptable option for the management of BOT in a younger patient. This analysis highlights the importance of complete comprehensive staging surgery of BOT even when fertility is preserved.

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Conflicts of Interest

There are no conflicts of interest.

References

1 Skírnisdóttir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960-2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer 2008;123(8):1897–1901
2 Tropé C, Kaern J. Management of borderline tumors of the ovary: state of the art. Semin Oncol 1998;25(3):372–380
3 Sherman ME, Mink PJ, Curtis R, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer 2004;100(5):1045–1052
4 Morris CR, Liu L, Rodriguez AO, Cress RD, Snipes K. Epidemiologic features of borderline ovarian tumors in California: a population-based study. Cancer Causes Control 2013;24(4):665–674
5 du Bois A, Ewald-Riegler N, de Gregorio N, et al. Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. Borderline tumours of the ovary: a cohort study of the arbeitsgmeinschaft gynäkologische onkologie (AGO) study group. Eur J Cancer 2013;49(8):1905–1914
6 Trillsch F, Mahner S, Woelber L, et al. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. Ann Oncol 2014;25(7):1320–1327
7 Song T, Lee YY, Choi CH, et al. Risk factors for progression to invasive carcinoma in patients with borderline ovarian tumors. Int J Gynecol Cancer 2014;24(7):1206–1214

8 Ren J, Peng Z, Yang K. A clinicopathologic multivariate analysis affecting recurrence of borderline ovarian tumors. Gynecol Oncol 2008;110(2):162–167
9 Cusidó M, Balagueró L, Hernandez G, et al; Section of Gynecologic Oncology and Breast Pathology of Spanish Federation of Gynecologic Oncology (SEGO). Results of the national survey of borderline ovarian tumors in Spain. Gynecol Oncol 2007;104(3):617–622
10 Camatte S, Morice P, Thoury A, et al. Impact of surgical staging in patients with macroscopic "stage I" ovarian borderline tumours: analysis of a continuous series of 101 cases. Eur J Cancer 2004;40(12):1842–1849
11 Hendricks A, Denny L, van Wijk L. An audit of the management of women with borderline ovarian tumours treated at Groote Schuur Hospital between 1984–2008. https://open.uct.ac.za/bitstream/handle/11427/25292/thesis_hsf_2017_hendricks_aneeqah.pdf?sequence=1&isAllowed=y
12 Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. Oncologist 2012;17(12):1515–1533
13 Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. J Clin Oncol 2007;25(20):2928–2937
14 Morice P, Camatte S, Wicart-Poque F, et al. Results of conservative management of epithelial malignant and borderline ovarian tumours. Hum Reprod Update 2003;9(2):185–192
15 Koskas M, Uzan C, Gouy S, et al. Prognostic factors of a large retrospective series of mucinous borderline tumors of the ovary (excluding peritoneal pseudomyxoma) Ann Surg Oncol 2011;18(1):40–48
16 Abascal-Saiz A, Sotillo-Mallo L, de Santiago J, Zapardiel I. Management of borderline ovarian tumours: a comprehensive review of the literature. Ecancermedicalscience 2014;8:403
17 Benito V, Lubrano A, Arencibia O, et al. Serous and mucinous borderline ovarian tumors: are there real differences between these two entities? Eur J Obstet Gynecol Reprod Biol 2010;153(2):188–192
18 Gungor T, Cetinkaya N, Yalcin H, et al. Retrospective evaluation of borderline ovarian tumors: single center experience of 183 cases. Arch Gynecol Obstet 2015;291(1):123–130