International Journal of Community Medicine and Public Health
Aziz AB et al. Int J Community Med Public Health. 2023 Jun;10(6):2031-2036
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20231678

Original Research Article

Borderline ovarian tumors: retrospective study and literature review

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Received: 29 March 2023
Revised: 02 May 2023
Accepted: 03 May 2023

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ABSTRACT

Background: Borderline Ovarian tumor are epithelial tumors, diagnosed in early stage with excellent prognosis. The risk of recurrence is matter of concern.
Methods: A retrospective, cross-sectional study conducted at OBGYN department of Aga khan hospital Karachi from 2002 to 2018.
Results: Seventy-three patients with BOT were enrolled with mean age of 40 years. Fertility sparing surgery (FSS) was performed in 35 (48%) while 38 (52%) underwent debulking surgery. Average pre-operative CA-125 IU level was 47 in FSS and 40 in debulking group. Laparotomy was the commonest surgery in both groups with 5 (14%) patients in FSS group having laparoscopy. In debulking group, 3 patients (8%) had residual disease. Majority of patients in both groups had stage 1 disease i.e., 34 (97%) and 34 (89%) respectively. Serous was the most common histological type in both groups while unilateral lesions were prevalent in the FSS group (83% vs. 68%). Recurrence was reported in 3(8.6%) patients in FSS, while 1 (2.6%) in debulking group. Mean time to recurrence was 57.13 months. Amongst the 4 recurrences, 3 patients had FSS and had unilateral tumor, ruptured capsule or surface disease. They had mucinous histology with negative cytology. One from debulking group had recurrence with bilateral tumor, serous histology and stage IIIC. Three patients (9%) conceived in FSS and had live births. The 5-year overall survival was 97.9%.
Conclusions: BOT have a favorable prognosis. Recurrences occur late in the trajectory of disease and hence regular follow-ups are important. They are common in mucinous tumors with external capsular involvement.

Keywords: Borderline ovarian tumour, survival, recurrence**,** fertility sparing surgery.

INTRODUCTION

Borderline ovarian tumors (BOT) are the diverse subdivision of epithelial ovarian tumors which consist of abnormal epithelial proliferation without stromal invasion. About 15% to 20% of all ovarian epithelial cell tumors are comprised of BOT. Because of their slow developing nature, these tumors are often known as tumors with low malignant potential These are also called tumors of low malignant potential because of their slow developing nature.[1] They display transitional histologic and biologic features between those of clearly benign and those of clearly malignant ovarian cancers.[2] The true incidence of BOT is not known. The annual incidence in Europe is estimated to range from 1.8 to 4.8 per 100,000 women. One third of these women are under the age of 40 years of age with apprehension to reserve their reproductive potential.[3] When compared to invasive epithelial ovarian malignancies, BOTs are detected at an earlier stage and have a better prognosis, with an overall 10-year survival rate of 83 % to 91%.[4] BOT are staged by same FIGO classification system as ovarian, fallopian tube and primary peritoneal cancer[1].They can be associated with peritoneal and lymph node spread. However, peritoneal disease from BOT is referred to as implants and not metastasis.[5] The commonest two subtypes of these tumors are serous (50%) and mucinous tumors (45%), having different features and clinical behavior. Other rare

subtypes include Endometroid, clear-cell and transitional cell (Brenner) histology.[3] The diagnosis of BOTs is established on histological inspection, while CA-125 values are typically normal or slightly elevated. The initial clinical symptoms are often nonspecific including pelvic discomfort or distension and almost 16%-30% patients with BOT are asymptomatic and diagnosed incidentally.[6] Their initial presentation is a benign entity, later they may be evident as either a more aggressive form or undergo malignant change. The absolute risk of malignant transformation of a previous BOT is 2% to 4%, usually as low-grade carcinoma. In exceptional cases of serous BOT, conversion in to high grade serous carcinoma may occur.[7]

Surgery is the cornerstone in the management of BOTs, but the surgical approach and the extent of the staging operation are up for controversy.[8] The standard treatment of BOTs is complete comprehensive surgical staging, including exploration of the entire abdominal cavity, total hysterectomy, bilateral Salpingo-oophorectomy, infracolic Omentectomy, peritoneal biopsies, peritoneal washings, and elimination of all visibly suspicious peritoneal lesions beside appendectomy in case of mucinous histology.[7] Fertility sparing surgery entails either cystectomy (unilateral or bilateral) or unilateral Salpingo-oophorectomy with preservation of the uterus and the contralateral adnexa along with complete surgical staging.[8] Factors significantly related with progression free survival described by Chen et al. are tumor diameter, mucinous histology, positive pelvic & para aortic lymph nodes, tumor stage, invasive implant, fertility sparing surgery and adjuvant chemotherapy.[9] Pelvic and para-aortic lymphadenectomy do not increase overall survival. [9] In a systematic review by Daraii. E et al, reported pooled estimate for spontaneous pregnancies following conservative surgery is 54%.[10]

Recurrence risk is 3% to 11% risk after standard or non-fertility sparing surgical treatment compared to 8.3% risk among women who undergo fertility sparing surgery. Factors predictive of recurrence in BOT include cyst rupture, bilateral tumor, micro papillary pattern, micro invasion and peritoneal implants.[9] Risk of late recurrence in BOTs progressively decreases with increase in the duration of progression free survival period. According to a Turkish Gynecologic Oncology Group study, recurrence rates are 10%, 19%, 10%, and 5% after 5 years, 10 years, 15 years, and more than 15 years, respectively.[11] Though less but the risk of recurrence, often in the form of invasive and occasional mortality associated with BOT remains a matter of concern for oncologists. Therefore, knowing the risk factors for better prediction of recurrence is important. This may help oncologists to individualize optimal treatment plan for BOT patients at particular risk of relapse. There is paucity of National data-based evidence on this aspect of ovarian tumors due to the relative rarity of borderline ovarian tumors. Therefore, this study's results will add up information about.

METHODS

This was a retrospective, cross-sectional study. The study population consisted of Women who were diagnosed, treated, and followed up as case of borderline ovarian tumor in Obstetrics & Gynecology Department of Aga Khan University Hospital Karachi. The study period was from July 1, 2002, to June 30, 2018. After institutional Ethical Review Committee (ERC) exemption was obtained, the electronic data and charts of all patients were reviewed, and the data were congregated on pre-formed structured Performa. Patients with incomplete medical records, 2 concurrent primaries and invasive carcinoma were excluded from the study. Statistical analysis was done by SPSS.20.0 software. Categorical variables were assessed by chi-square test. Quantitative variables were compared by student's t test. The recurrence and fertility outcomes were analyzed distinctly using potential risk factors and favoring factors, respectively. The Kaplan Meier curve was used to analyze the overall survival and difference assessed by log-rank test. P value of 0.05 was considered statistically significant.

RESULTS

A total of 73 patients with borderline ovarian tumor analyzed in this study. Out of these patients, 35 patients had fertility sparing surgery while 38 underwent Debulking surgery. Their clinic-pathological characteristics are listed in (Table 1).

Table 1: Baseline characteristics (n=73).

Variables	Estimates, N (%)
Age (years)	40 (32-54)*
Range (years)	17-84
Marital Status	
Single	20 (27.4)
Married	53 (72.6)
Parity	
Nulliparous	32 (43.8)
Multiparous	42 (56.2)
Infertility history	9 (12.3)
Family history of ovarian cancer	1 (1.4)
Family history of breast cancer	7 (9.6)
Preoperative CA125 level	40.19 (20.62-79.79)*
FIGO stage†	
IA-IC	68 (93.2)
IIIB-C	5 (6.8)
Site of lesion	
Unilateral	55 (75.3)
Bilateral	18 (24.7)
Tumor size	10 (6.5-19)*
Range	2-34
Size of tumor (cm)	
≤10	37 (50.7)
>10	36 (49.3)

Data are presented as n (%) and *Median (25-75th Percentile). †IA=49 IB=1, IC=18, IIIB=2, IIIC=3.

Table 2: Treatment modalities, recurrence, and mortality (n=73).

Variables	Estimates, N (%)
Surgical approach	
Laparotomy	68 (93.2)
Laparoscopy	5 (6.8)
Type of surgery	
Fertility sparing surgery	35 (47.9)
Debulking surgery	38 (52.1)
Tumor capsule	
Intact	55 (75.3)
Rupture	14 (19.2)
Surface disease	4 (5.5)
Histology type	
Serous	38 (52.1)
Mucinous	30 (41.1)
Seromucinous	3 (4.1)
Others	2 (2.1)
Histological features in serous type (N=38)	
Micropapillary	27 (71.1)
Microinvasion	7(18.4)
Not reported	4 (10.5)
Histological features in mucinous type (N=30)	
Intraepithelial neoplasia	
Yes	13 (43.3)
No	17 (56.7)
Cytology	
Positive	12 (16.4)
Negative	53 (72.6)
Not taken	8 11.0)
Peritoneal implants	6 (8.2)
Pelvic positive lymph nodes	1 (1.4)
Appendectomy	8 (11)
Residual disease <1 cm	3 (4.1)
Adjuvant chemotherapy	4 (5.5)
Recurrence	4 (5.5)
Mortality	1 (1.4)
Restaging or completion surgery	7 (9.6)
Duration of follow-up in months	33 (10.29-68.93)*

*Median (25-75th Percentile)

The mean age of the study population was 34 years in FSS group while 53 years in debulking group. Pre-operative CA-125 IU level was 47 (23.7-76.1) in FSS group and 40 (13.8-73.6) in debulking group. Majority of the study population had FIGO stage 1 in both the groups. Out of 35 patients in FSS group, 34 (97.1%) had stage IA-IC, and 1 (2.9%) patient had stage IIIB. The distribution of stages amongst the Debulking group were as follows: stage IA-IC, 34(89.5 percent), and 4 (10.5%) in stage IIIB-IIIC with average tumor size was 12cm (6.8-20), with 26 (68.4%) unilateral and 6 (17.1%) bilateral tumors. In the FSS group, the average tumor size was 9.6cm (6.5-16), with 29 (82.9%) tumors were unilateral and 12 (31.6%) bilateral. The most common histological type was serous in both the study groups with 17 (48.6%) patients in FSS group and 21 (55.3%) in Debulking group. Mucinous was the second most common histology in both the groups with 17 (45%) and 13 (37%) patients in Debulking and FSS groups respectively. In addition, the proportion of patients underwent FSS had intact tumor capsule in 23(65.7%) patients and ruptured in 10 (28.6%) and 2 (5.7%) with surface disease whereas in Debulking group, the tumor capsule was intact in 32 (84.2%), 4 (10.5%) ruptured capsule and 2 (5.3%) with surface disease. Cytology was positive in 8 (21%) patients in Debulking group and 4 (11.4%) patients in FSS group.

It was negative in 28 (80%) and 25 (65.8%) patients of FSS and Debulking groups retrospectively. Peritoneal implants were positive in 1 (2.9%) patient in FSS and 5 (13.2%) patients in Debulking group. Pelvic lymph node was not positive in any patient who underwent FSS while they were positive in only 1 (2.6%) patient in Debulking group. Appendectomy was performed in 8 patients of the study population with 1 (2.9%) in FSS and 7 (18.4%) patients in Debulking group.

Laparotomy was the usual surgical method in 30 (85.7%) patients in FSS and 38 (100%) patients who underwent debulking. Only 5 (14.3%) patients in FSS group had laparoscopic surgery. There was no residual disease reported in any patient of the FSS group while in Debulking group 3 (7.9%) patients had residual disease which was less than 1 cm (Table 2-3).

Recurrence was reported in total 4 cases, 3(8.6%) of FSS group and 1 (2.6%) in Debulking group. The total duration of follow up in months was 32.38 (10.64-95.19) in FSS group and 38.16 (10.29-56.94) in debulking group. Recurrence-free survival rate of 89.7 months and overall survival of 97.9% in this study (Figure 1-2) The fertility outcome was 9% in the study with 3 live births (Figure 3).

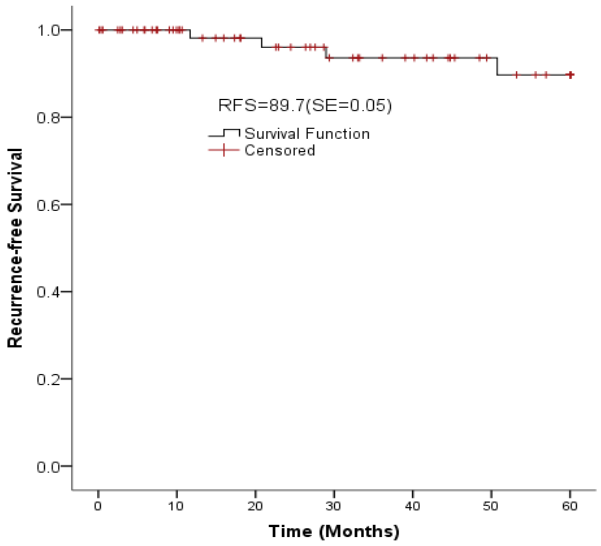

Figure 1: Kaplan Meir curve showing the recurrence free survival (RFS) Mean recurrence time = 57.13 (SE=1.43).

Table 3: Comparison of characteristics between fertility sparing vs. debulking surgery.

Variables	Fertility sparing surgery, N=35	Debulking surgery, N=38	P value
Age (years)*	34 (27-40)	53.5 (39.5-65.25)	0.0005
Preoperative CA-125 Level IU*	47 (23.7-76.1)	40 (13.8-73.6)	0.566
FIGO stage			0.195
IA-C	34 (97.1)	34 (89.5)	
IIIB-C	1 (2.9)	4 (10.5)	
Size of Tumor (cm)	9.6 (6.5-16)	12 (6.8-20)	0.325
Site			
Unilateral	29 (82.9)	26 (68.4)	0.153
Bilateral	6 (17.1)	12 (31.6)	
Histology			0.074
Serous	17 (48.6)	21 (55.3)	
Mucinous	13 (37)	17 (45)	
Seromucinous	3 (11.1)	0 (0)	
Others	2 (5.7)	0 (0)	
Tumor capsule			0.120
Intact	23 (65.7)	32 (84.2)	
Rupture	10 (28.6)	4 (10.5)	
Surface disease	2 (5.7)	2 (5.3)	
Cytology			0.295
Positive	4 (11.4)	8 (21.1)	
Negative	28 (80)	25 (65.8)	
Not done	3 (8.6)	5 (13.2)	
Peritoneal implants	1 (2.9)	5 (13.2)	0.201
Positive pelvic lymph nodes	0 (0)	2.6 (1/26)	0.999
Appendectomy	1 (2.9)	7 (18.4)	0.036
Surgical approach			
Laparotomy	30 (85.7)	38 (100)	0.022
Laparoscopy	5 (14.3)	0 (0)	
Residual disease <1 cm	0 (0)	3 (7.9)	0.241
Restaging/completion surgery	3 (8.6)	4 (10.5)	0.998
Adjuvant chemotherapy	1 (2.9)	3 (7.9)	0.616
Recurrence	3 (8.6)	1 (2.6)	0.344
Mortality	1 (2.9)	0 (0)	0.478
Duration of follow-up in months*	32.38 (10.64-95.19)	38.16 (10.29-56.94)	0.446

*Median (25-75th Percentile)

DISCUSSION

BOT implies a self-determining group of ovarian tumors that exhibit aberrant epithelial proliferation exclusive of stromal invasion.

It constitutes 10% to 20% of all ovarian epithelial tumors and commonly occur in early ages accompanying favorable prognosis if comprehensive staging is performed.[12] In an analysis of 15 studies, which comprised a total of 948 patients, 69.6% (660) of borderline tumors occurred in stage I.

Disease spread within the pelvis or beyond (FIGO stages II-III) is rarely seen at the time of diagnosis while advanced stage disease (FIGO stage IV) is an exception.[13,14] This is analogous to our findings, in which 93% patients exhibited stage 1, 6.8% with stage IIIB -IIIC, and none had stage IV disease. The primary treatment of BOT is surgical. Optimum staging permits accurate extent of the disease to determine prognosis. There has been advancement in the treatment of BOTs, from extensive surgery a few decades ago to a more conservative approach currently. As an acceptable standard of care, fertility-preserving surgery entails the preservation of the uterus and at least one ovary. Comprehensive staging is necessary to figure out any invasive implants in such patients which may entail the need of adjuvant treatment.

Preoperatively, the extent of surgery must be explained to the patient, highlighting that available data predict a higher probability of recurrence after FSS (10% to 20% against 5% for debulking surgery.[15]

These figures resemble to our data, in which recurrence was documented in four instances, three (8.6%) in the FSS group and only one (2.6%) in the Debulking group. Laparoscopic management of BOT is associated with a higher possibility of cyst rupture and incomplete staging. According to a review by du Bois et al a higher recurrence

rate was observed in conservative surgery done laparoscopically as compared to open approach (14.9 vs. 7.7%).

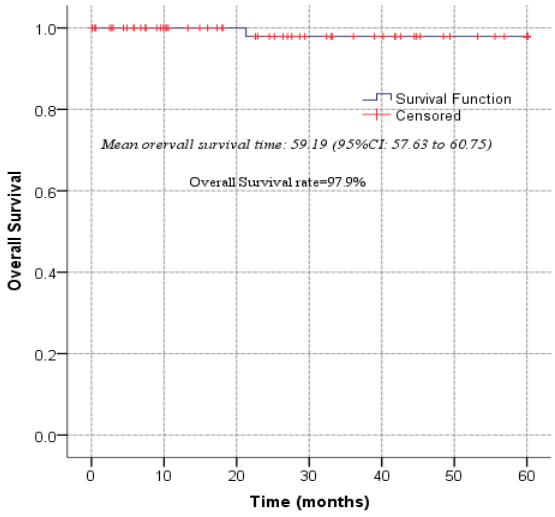

Figure 2: Kaplan–Meier curves: five years' overall survival.

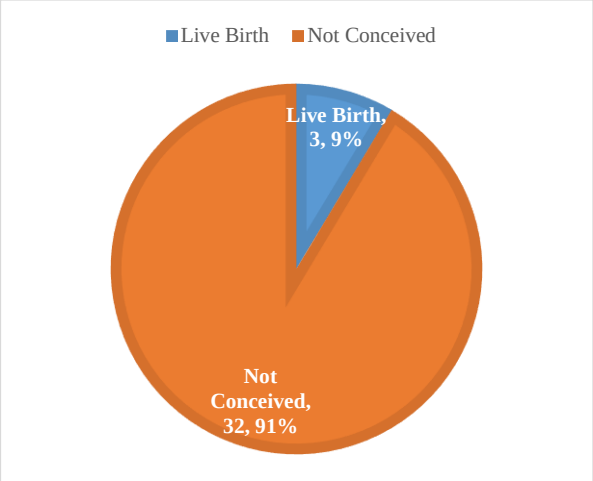

Figure 3: Fertility outcome.

However, laparoscopy appears to be a feasible and appealing option, with decreased morbidity and fewer adhesions, both of which are essential for better fertility outcomes.[16] The surgical approach (laparoscopic vs. laparotomy) did not seem to affect the progression-free interval and rate of relapse, in an Italian and a French multicenter study.[12,13,17] Our findings differed from these published studies as two of the four recurrent cases of BOT in the FSS group had laparotomy and only one had laparoscopy making no association of laparoscopy to recurrence. Analysis of factors associated with recurrence showed that initial FIGO stage could be anywhere from IA to IIIC. Out of total 73 patients in our study group 3(4.1%) had local recurrence amongst FSS group and 1 (1.4%) had distant recurrence from the debulking group. Mucinous tumors size greater than 10 cm tends to recur more however peritoneal cytology had no relationship with recurrence. The German ROBOT study found a higher recurrence rate without any increase in mortality risk.[12] Our study reported 5.5 percent recurrence after a median follow-up of 33 months and one mortality reported in this series which is proportionate with those reported in the literature.

The relationship between CA-125 level with BOTs is variable. In the systematic review by du Bois et al., patients with BOT had normal levels of CA-125 in 53.8% of patients. Similar results were observed in the multi-center prospective international ovarian trial analysis (IOTA) in which 5% of 1,918 patients were BOT and approximately half of these had normal CA125 levels. The CA125 median value touched 35 U/mL (interquartile range: 19-105 U/ml) in patients with newly detected BOTs.[18] Our data showed association of initial tumor markers level of CA-125 as significant predictors for the relapse in BOTs. In 4 recurrences, CA125 level was reasonably high in patient who had recurrence, 69.5 (25.6-240.8) verifying that it is an important prognosticator of relapse during surveillance. In the literature, spontaneous pregnancy has been documented in 50% of patients after conservative surgery, with no worsening of the survival rate.[15] However, patients with BOTs, commonly experience infertility as it has been showed by a study in which up to 35% of these patients had history of fertility problems prior to therapy.[19] in our analysis, this percentage was only 9%. Conservative surgery for patients over the age of 40 should be addressed with caution. There were no pregnancies in this age range in a major multicenter study published by Fauvet et al.[17] The features supporting successful fertility outcomes with 3 live births (9%) in this study was FIGO sage 1A, unilateral tumor, negative cytology, cystectomy, and no previous history of infertility at initial presentation. As per prior reports, patients with BOT have a 5-year and 10-year survival rate of 95 and 93 percent, respectively. In addition, the mortality of BOT is low.[20] We had an equivalent recurrence-free survival rate of 89.7 months and overall survival of 97.9% in this study.

Limitations

There are certain limitations of our study The foremost limitation is retrospective data which is always a threat to both internal and external validity of the study. Secondly, it is taken from a single, large teaching hospital of one city only.

CONCLUSION

BOT has an excellent prognosis and overall survival. Depending on the patient's age and fertility desire, it can be managed with FSS or debulking surgery. For those experiencing FSS, laparoscopic surgery is a reasonable substitute. Most unilateral mucinous tumors with FSS relapse. During surveillance, it's critical to keep an eye on CA125 levels. Patients with stage IA disease have favorable fertility outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Aziz AB, Sikandar N, Aziz H, Chishti U. Borderline ovarian tumors: retrospective study and literature review. Int J Community Med Public Health 2023;10:2031-6.