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Clinical report

Clinical characteristics and outcome for treatment for borderline ovarian tumor in King Chulalongkorn Memorial Hospital

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Background: Borderline ovarian tumor (BOT) is a distinct diagnosis which comprises 5%–15% of epithelial ovarian tumor. Borderline ovarian tumor is characterized histologically as an epithelial tumor with stratified growth pattern without destructive stromal invasion. From observation, BOT in our institution is more common in the mucinous cell type, as distinct from that reported in previous reviews.
Objective: This study was conducted to evaluate characteristics, treatment outcome and recurrence of BOT in our institution.
Methods: A retrospective review was made of the medical records of BOT patients to collect data. From 2006 to 2010, all 55 cases of BOT were reviewed from the aspect of general characteristics, presenting symptoms, tumor markers, pathologic diagnosis, operations, treatment outcome, and recurrence.
Results: The median age of the 55 BOT patients was 42 years. The common presenting symptoms were palpable mass, abdominal discomfort, and pelvic pain. One fourth of the patients had no symptoms. Mucinous cells were the most common subtype histologically (72.7%). Serous cell subtype were found in 21.8%. The most common surgical procedure was salpingo-oophorectomy. Median follow up time was 38 months. There was recurrence of 5 cases (9.1%) and recurrence was more common in the patients with a serous cell subtype and those who had residual tumors after primary surgery. A higher stage of disease was also associated with a greater risk of recurrence.
Conclusion: While most previous studies showed that a serous cell subtype was the most common subtype, our study found the mucinous cell subtype was the most common at our institution. Recurrence was quite common in patients with the mucinous cell subtype with microinvasion, and was more common in patients with residual tumors after primary surgery. From the aspect of recurrence, these findings were not different from those of previous studies. The optimal treatment of recurrence remains controversial.

Keywords: Borderline ovarian tumor, microinvasive, mucinous, outcome, recurrence, serous

Borderline ovarian tumor (BOT) is epithelial ovarian tumor which has a stratified growth pattern without destructive stromal invasion [1, 2]. BOT comprises up to 5%–15% of all ovarian epithelial neoplasms [1]. Synonyms for BOT are tumor of low malignant potential, tumor of borderline malignancy, and atypical proliferative ovarian tumor. They often affect younger patients more than epithelial ovarian cancer. The tumor has indolent behavior and late recurrence. Patients with BOTs have a longer survival time [3]. Nearly all reviews reported the 5 year survival as nearly 100% [4]. At the time of diagnosis, 70% of BOTs were at stage I, and had a 5 year survival about 95%–97% [3]. Serous and mucinous neoplasms comprise the majority of BOTs [2]. Serous borderline ovarian tumor is the most common BOT worldwide. These BOTs may behave in an aggressive fashion, associated with peritoneal implant and regional lymphadenopathy. Serous BOTs comprise about 50%–65% of BOTs, and mucinous BOTs are involved in 30%–40%, and 10% involve other histological cell types [5]. There are several studies that describe the cytogenetic, epidemiologic, and natural history characteristics of BOTs. This retrospective review was conducted to evaluate the clinical characteristics, treatment outcome, and recurrence of BOTs at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

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Materials and methods

Following approval of this retrospective study by our institutional ethics committee, a chart review was performed. All the charts of the patients diagnosed as having borderline ovarian tumor and ovarian tumor of low malignant potential were reviewed. We retrospectively identified cases of BOTs in 55 patients who were treated and followed up at King Chulalongkorn Memorial Hospital from January 2006 to December 2010. Data regarding the general characteristics, presenting symptoms, tumor markers, pathological diagnosis, surgery and outcome including recurrence were collected. Criteria for diagnosis of BOTs were:

1. Epithelial hyperplasia which is in the forms of pseudostratification, tufting, cribriform and micropapillary architectures.
2. There is nuclear atypia and increased mitotic activity.
3. There is a detached cell cluster.
4. There is absence of stromal invasion in the primary tumor [6-8].

The characteristic data included age, BMI, underlying disease, and ultrasound findings. Tumor markers included CA 125, CEA, and CA19-9 were assessed at the time of diagnosis. Pathological diagnosis was classified according to cell type and appearance of microinvasion. Surgery was classified as cystectomy, salpingo-oophorectomy, TAH with BSO, TAH BSO with surgical staging, and SO with surgical staging. Follow-up period and recurrences were also included in the data collection. Characteristics of cases and patients in the recurrence group were identified.

After all data were collected, we conducted a statistical analysis. All data were analyzed using mean, mode, median percent and SD.

Results

General characteristics of the 55 BOT patients were identified and are shown in **Table 1**. Their average age was 42 years (from 13 to 89 years). Mean BMI was 23.38 kg/m^2. Most the patients were Thai. The mean tumor size was 13.39 cm (from 3 to 37 cm, SD 6.44). The most common presenting symptom was palpable mass, which was found in 38.2% of the patients, 18.2% had abdominal discomfort, 16.4% developed pelvic pain, and 27.2% of the patients had no symptoms. Nearly half of the patients (45.5%) were found to have mutiloculated cysts on ultrasound imaging, 36.4% of patients revealed a uniloculated cyst, 27.3% of the ultrasonography identified a solid area and 54.5% was no solid area. Tumor markers for those patients were reviewed, mean CA 125 level was 61.44 (6.96–565.2, 103.02). Mean CA19-9 level was 137.82 (0.6–1000, 270.57). Mean CEA level was 12.27 (0.35–81.24, 23.36).

The operative data are shown in **Table 2**. The most common procedure was unilateral salpingo-oophorectomy undergone by 36.4% of the patients. The other procedures were TAHBSO, TAHBSO with surgical staging, salpingo-oophorectomy with surgical staging undergone by 27.3%, 23.7%, and 9.1% of patients respectively. Incidental appendectomy was performed in 63.6% of the cases and all of the pathological reports of the appendix were negative. Most of the patients were diagnosed as having stage I (92.7%). The pathological reports were analyzed. Mucinous cell involvement was the most common type and comprised 72.7% of the patients. Serous cell involvement was found in 21.8% of the patients, and the other cell types were mucinous with microinvasion (3.6%), and serous with microinvasion (1.8%). Most of the patients did not receive adjuvant chemotherapy (96.4%).

Table 1. General characteristics of all borderline ovarian tumors in King Chulalongkorn Memorial Hospital during 2006–2010

Character	Mean	SD	Min	Max
Age (y)	42	16	13	89
BMI (kg/m^2)	23.37	4.66	17.6	31.21
Tumor size (cm)	13.39	6.44	3	37
CA 125	61.44	103.02	6.96	565.2
CA 19-9	137.82	270.57	0.60	1000
CEA	12.27	23.36	0.35	81.24
Follow-up (m)	40	16	14	71

Table 2. Presenting symptoms, findings, and surgical data in borderline ovarian tumor patients

	Number	Percent (%)
Stage		
I	51	92.7
III	4	7.3
Presenting symptoms		
None	13	23.6
Palpable mass	21	38.2
Abdominal Discomfort	10	18.2
Pelvic pain	9	16.4
Pressure pain	1	1.8
Other	1	1.8
Ultrasound finding		
Uniloculate	20	36.4
Multiloculate	25	45.5
Missing	10	18.2
Surgical Procedure		
SO	20	36.4
TAHBSO	15	27.3
TAH BSO and staging	13	23.7
SO and staging	3	5.5
BSO and staging	2	3.6
LAVH and SO	1	1.8
Incidental appendectomy	20	36.4
Residual disease		
None	51	92.7
<2 cm	1	1.8
2 cm or more	3	5.5
Histological cell type		
Mucinous	40	72.7
Serous	12	21.8
Mucinous with microinvasive	2	3.6
Serous with microinvasive	1	1.8
Adjuvant treatment	2	3.6

The follow-up appointments were made every 3 months in first two years after treatment and every 6 months for the next 3 years. Median time to follow-up was 38 months in this series (range 14–71 months). Recurrence was detected in 5 (9.1%) of the total 55 patients. Characteristics of the recurrent patients were reviewed and the results are presented in **Table 3**. In most of the recurrent cases, primary diagnosis was stage I (80%). Three patients (60%) underwent salpingo-oophorectomy for the first operation. The other cases had TAHBSO and TAHBSO with surgical staging. From pathological findings 40% of recurrence arose from a mucinous cell type, 40% from a serous cell type, and 20% from mucinous with microinvasion.

Discussion

BOT is associated with a good prognosis. The diagnosis must be finalized after the surgery is completed and pathology is reported. Management of this kind of ovarian tumor differs from that for both benign and malignant tumors. Therefore, BOT requires high index of suspicion for provisional diagnosis to establish plan for proper management. The key must be the concern regarding risk factors and clinical presentation, which may vary according to the population in different countries.

According to previous reviews, serous cells are the most common histologic subtype of BOTs [2, 5, 7, 9, 10]. Only few studies showed that mucinous cell involvement was more common. In our institution we

Table 3. Demonstration data for recurrence cases

	Number	Percent (%)
Recurrent	5	9.1
Recurrence from previous stage		
1	4	80
3	1	20
Previous surgery of recurrence case		
SO	3	60
TAH BSO	1	20
TAH BSO and staging	1	20
Pathological cell type of recurrence		
Mucinous	2	40
Serous	2	40
Mucinous with microinvasion	1	20

found the mucinous subtype comprised about 72.7% of all BOTs. The mean age at presentation was 42 years old, which is rather younger than previous studies.

We found the most common clinical presentation was a palpable mass, which was different from previous studies that found abdominal pain and distention were most common [1, 3, 4]. Interestingly, we found about a quater of the patients had no symptoms, as comparable to other studies. Therefore, it might be easy for patients to palpate the suspected abdominal mass themselves. Although ultrasonography is widely used by gynecologists and is very useful in identifying the mass, this method is not currently able to predict the final pathology of the ovarian tumor, particularly of BOTs. From our study, we found a solid area in the ovarian cyst in only 27.3% of cases and this could not be differentiated from malignancy. Nowadays, preoperative transvaginal color Doppler ultrasonography has been used to predict the possibility of malignancy in ovarian tumors. The rate of detection of intratumoral blood flow in BOTs (90%) is similar to that of ovarian cancer (92%). The resistance and pulsatility indexes are also significantly reduced in cancer and BOTs compared with that of benign tumors. However, transvaginal color Doppler ultrasonography remains limited in its ability to differentiate the BOTs from ovarian cancers [9, 10]. Tumor markers have important roles in the diagnosis and follow-up care of the patients with BOTs. High levels of tumor markers, particularly CA 125 and CA 19-9, may indicate a larger tumor size. Elevation of serum CA 125 may suggest a serous subtype, while a high level of serum CA 19-9 and CEA may indicate mucinous BOTs [10]. In this study, we were not able to reach a conclusion regarding the significance of tumor markers because of the limited number of patients and unavailability of the tumor marker data for some patients.

The guidelines for standard surgical treatment of BOTs are similar to those for ovarian cancer and include peritoneal washing, hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, complete peritoneal resection of macroscopic lesions or multiple peritoneal biopsies, and pelvic or para-aortic lymphadenectomy, or both. Appendectomy should also be performed in cases of mucinous BOTs [7, 9-11]. However, patients with borderline ovarian tumors tend to be younger than patients with ovarian cancer. Therefore, fertility may still be an important issue for these patients. Previous studies have suggested the safety of conservative surgery with unilateral salpingo-oophorectomy for patients with stage I BOTs, including in patients with advanced-stage disease [11, 12]. From our study, most of the patients were diagnosed with stage I tumors and the most common procedure was unilateral salpingo-oophorectomy conducted in 36.4% of the patients. The other procedures were TAHBSO, TAHBSO with surgical staging, and unilateral SO with surgical staging. The procedure chosen was varied according to the age, the need for fertility, and intraoperative findings. Unfortunately, the use of frozen sections for intraoperative diagnosis BOTs remains limited. Pooled data from three previous studies reported that the agreement between frozen section diagnosis and definitive histology was

observed in 199/317 (62.8%) patients, yielding an overall sensitivity and a PPV of 71.1% and 84.3%, respectively. Overdiagnoses and underdiagnoses were identified in 21/317 (6.6%) and in 97/317 (30.6%) cases, respectively [13-15]. Because of these high numbers of over- and underdiagnoses it is a valuable option to postpone definitive surgical management of BOTs until a final histological report is available, particularly in young patients for whom fertility or ovarian function are important. In our retrospective study, there was no patient whose tissue was sent for frozen section analysis. Incidental appendectomy was performed according to the standard guidelines in 63.6% of patients with a mucinous histologic subtype and all of the pathological reports of the appendix were negative for tumor.

Trop et al. [11] studied adjuvant chemotherapy or radiotherapy for BOTs in stage I, and Morice et al. [12] studied adjuvant chemotherapy or radiotherapy in advanced stage BOTs. Both of these studies showed no benefit of adjuvant treatment, which often resulted in unnecessary toxicity [16, 17]. In our study, most of the patients did not receive adjuvant chemotherapy (96.4%). Previous studies reported recurrence rates from 10% to 30% following conservative surgery, with the majority involving the development of a second BOT [18-23]. Higher recurrence rates associated with BOTs have also been attributed to malignant transformation, although the overall risk of this occurring is quite low [22. 23]. After completion of primary treatment, the patients in our study were followed up for 14–71 months (median 38 months). There were 9.1% of patients that had recurrence. All of the patients in the study are still alive, which is comparable to the 99% survival rates documented in previous studies [3, 4, 22, 23].

We present retrospective data from patients with BOT who were initially treated and followed up at a single institution. We recognize the limitation of our study because of the size of the patient population and the retrospective nature of this study. However, there has never been any study that reviewed the histologic subtypes, recurrence, and survival for such a rare disease in Thailand. This study may provide significant basic data for additional study of BOT patients that attempts to underscore optimal treatment.

Conclusion

From our study data, BOT involving a mucinous cell type was more common than the serous cell subtype, as distinct from other studies. However, prognosis and five-year survival data were comparable to other studies. The recurrence rate found in our study was comparable with previous studies. Because of its retrospective nature, our study has some limitations. Additional studies may provide more in depth of data, especially in preoperative diagnosis options that can provide information for surgical planning.

The authors have no conflicts of interest to report.

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