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Original Research

Survival Outcomes and Prognostic Factors of Borderline Ovarian Tumors

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Background and Objective: Borderline ovarian tumor (BOT) is a distinct but heterogeneous group of tumors defined by histopathology as atypical epithelial proliferation without stromal invasion. Women with BOT are usually younger than those with invasive carcinoma. This study aimed to evaluate the survival outcomes and prognostic factors of patients with BOT in a single institute in the northern region of Thailand.
Methods: The medical records of patients with BOT who were treated at Chiang Mai University Hospital between January 1, 2008 and December 31, 2019 were reviewed. The survival outcomes were analyzed by the Kaplan-Meier method and prognostic factors were analyzed by univariate and multivariate approaches.
Results: 168 patients with BOT were enrolled in the study. The median age was 48.8 years. At the median follow-up time of 25.4 months, 9 patients (5.3%) developed recurrence and 2 (1.1%) experienced progression to invasive carcinoma. The 5-year progression-free survival (PFS) and overall survival were 93.2% and 97.4%, respectively. By univariate analysis, advanced stage (p=0.02), tumor size smaller than 10 cm (p=0.03), conservative surgery (p=0.03), and bilateral tumors (p=0.07) were significantly associated with worse PFS. Hysterectomy was a protective factor for recurrence with the hazard ratio of 0.09 (95% CI, 0.01 – 0.77; p= 0.03). Cell types, pelvic lymphadenectomy, micro-invasion, and non-invasive peritoneal implant did not significantly affect PFS. By multivariate analysis, early stage (p=0.01), tumor size larger than 10 cm (p=0.04), and hysterectomy (p=0.03) were significantly associated with better survival.
Conclusion: Patients with BOT had excellent survival outcomes. Tumor size of larger than 10 cm, early-stage disease, and hysterectomy were significant prognostic factors for better survival outcomes. Conservative surgery should be offered to patients who desire to preserve future fertility and long-term follow-up is needed to assure recurrence - free.

Introduction

Borderline ovarian tumor (BOT) or atypical proliferative tumor is once known as a tumor of low malignant potential (LMP). The diagnosis of BOT is based on pathological findings of atypical proliferation as seen in epithelial ovarian cancer, without stromal invasion. Occasionally, a non-invasive peritoneal implant could be found in patients with BOT. According to WHO classification in2014, a micro-invasion has been reported, in which the stromal invasion is observed less than 5 mm in the greatest linear dimension [1].

BOT is the tumor of a young age group and one-third of them are under 40 years of age [2, 3]. Most patients with BOT present at an early stage, and the prognosis is generally favorable. The pathology of BOT is classified into 6 subtypes in which the most prevalent type is serous followed

by mucinous, whereas endometrioid, clear cell, Brenner, and mixed sero-mucinous types are rarely found [1, 4].

Treatment for BOT depends on fertility desire. For patients who no longer need to preserve future fertility, complete surgical resection is usually performed as the same standard treatment for epithelial ovarian cancer. A certain study noted that in BOT, pelvic lymph node dissection is not necessary to perform as there is no benefit in improving the survival rate [5]. For patients who need to preserve future childbearing, fertility-sparing surgery should be offered by performing unilateral salpingo-oophorectomy (SO), sparing uterus, and contralateral normal ovary. Ovarian cystectomy could be performed in the setting of patients who have undergone contralateral SO or tumors involve bilateral ovaries without minimizing pregnancy rate [6]. However, the recurrence rate in patients undergoing ovarian cystectomy was significantly higher than those undergoing SO [7]. Adjuvant chemotherapy remains a controversial issue for BOT [4]. One study reported that chemotherapy was associated with worse survival outcomes [8].

In general, the recurrence rate of BOT patients is quite low with adequate follow up protocol. However, several factors have been identified as an increased risk of recurrence, i.e., conservative surgery, suboptimal surgery, non-invasive peritoneal implant, micro-invasion, and micropapillary architecture [9, 10].

This study was conducted to evaluate the survival outcomes and to identify the prognostic factors of patients with BOT undergoing surgical treatment at Chiang Mai University Hospital in the northern region of Thailand.

Materials and Methods

After approval of the Research Ethics Committee of Chiang Mai University Hospital (CMUH), the data were collected by retrospective review from January 1, 2008, to December 31, 2019 at CMUH, Chiang Mai, Thailand. The study population was women with BOT diagnosed from pathological examination and received treatment at the CMUH. The pathology slides were reviewed by gynecologic pathologists if the patients were referred from other hospitals.

Patients with malignant ovarian tumors, other concurrent malignancy, and incomplete medical records were excluded. The medical records including demographic data, preoperative tumor markers (CA125, CA19-9, and CEA), pathological characteristics (cell subtypes, non-invasive implants, micro-invasion) were retrieved from the electronic database of gynecologic oncology units.

The surgical procedure varied depending on the surgeon’s discretion, the frozen section results, and intraoperative findings. In cases with fertility desire, conservative surgery was carried out by performing unilateral SO, preserving contralateral normal ovary without hysterectomy. Hysterectomy with bilateral SO was defined as definitive surgery, while omentectomy, lymphadenectomy, and peritoneal biopsy were defined as surgical staging procedures.

All patients were followed every 3 months during the first year of surgery, every 4 months in year 2, every 6 months in year 3-5, and then yearly after year 5. Surveillance included clinical examination, pelvic examination, and tumor markers. Pelvic ultrasound was performed instead in those who were not able to undergo pelvic examination. CT scans or MRIs were used in patients with suspected recurrent diseases. Progression-free survival was the duration since the surgery to the presence of recurrent diseases and overall survival was the duration since the surgery until death.

Statistical analyses were performed using STATA version 15 (College Station, TX: StataCorp LLC.). Descriptive statistics were reported by median (interquartile range) for the continuous variables

and frequency (percentage) for categorical variables. Univariate and multivariate analyses were used to identify prognostic factors in the progression-free survival of BOT. The factors with a p-value of ≤ 0.10 in the univariate analysis were further analyzed in multivariate logistic regression models. The survival function was estimated by the Kaplan-Meier method and distribution for each group was compared by the log-rank test. A p-value of ≤ 0.05 was considered statistically significant.

Results

During the study period, 197 patients with BOT were identified in the database. Eighteen patients were excluded after pathological review, i.e., invasive epithelial ovarian cancer (7), benign mucinous cystadenoma (1), concurrent cancer (8), mucinous BOT from gastro-intestinal malignancy metastases (2). Six patients had incomplete medical records and 5 were lost to follow-up after the operation. Therefore, 168 patients were eligible for analysis. The clinical characteristics are shown in Table 1.

Characteristics	Number (%) or Median (Range)*
Age (Years)	48.4 (10.5-79.1) *
< 50	91 (54)
≥ 50	77 (46)
CA 125 (U/mL) (n=143)	52 (26.3-143.3)
< 35	55 (38)
≥ 35	90 (62)
CA 19-9 (U/mL) (n=137)	22.6 (6.6-119.1)
< 39	86 (62)
≥ 39	52 (38)
CEA (ng/ml) (n=136)	2.0 (1.1-4.6)
< 5.2	107 (78)
≥ 5.2	30 (22)
Primary treatment	
Definitive surgery	123 (73)
Conservative surgery	45 (27)
Pelvic lymphadenectomy	
No	105 (62)
Yes	63 (38)
Para-aortic lymphadenectomy	
No	144 (86)
Yes	24 (14)
Adjuvant chemotherapy	
No	153 (91)
Yes	15 (9)

Table 1. Clinical Characteristics of 168 Patients with Borderline Ovarian Tumor.

*Descriptive statistics were reported by median (interquartile range) for the continuous variables and frequency (percentage) for categorical variables; * Age was described by median (minimum-maximum)

Among 168 patients, 91 (54%) patients were younger than 50 years old. Elevated serum CA125 (> 35 U/mL) was noted in 90 (62%) patients. High serum CA19-9 (> 39 U/mL) and serum CEA (> 5.2 ng/ml) were found in 52 (38%) and 30 (22%) patients, respectively. Definitive surgery was performed in 123 patients (73%), while conservative surgery was carried out in 45 (27%). Pelvic

and para-aortic lymphadenectomy was performed in 63 (38%) and 24 (14%) patients, respectively. Adjuvant chemotherapy with paclitaxel with carboplatin was administered in 15 patients (9%).

Tumor characteristics are shown in Table 2.

Variables	Number of patients (%)
Cell type	
Endometrioid	8 (5)
Mucinous	118 (70)
Serous	40 (24)
Mixed	2 (1)
Stage	
I	156 (93)
II-III	12 (7)
Tumor size (cm) (n=166)	
≤ 10	30 (18)
> 10	136 (82)
Pelvic lymph node involvement (n=63)	
No	61 (97)
Yes	2 (3)
Para-aortic lymph node involvement (n=24)	
No	24 (100)
Yes	0 (0)
Micro-invasion	
No	137 (82)
Yes	31 (19)
Non-invasive implant	
No	152 (91)
Yes	16 (10)
Laterality	
Unilateral	151 (90)
Bilateral	17 (10)

Table 2. Tumor Characteristics of 168 Patients with Borderline Ovarian Tumor.

Descriptive statistics were reported by frequency (percentage) for categorical variables.

The most common cell type of BOT was mucinous (70%) followed by serous (24%) and endometrioid (5%). One hundred and fifty-six (93%) patients had stage I BOT while the remaining 12 (7%) had stage II and III diseases. Eighty-two percent of the patients had tumor size larger than 10 cm. The average tumor size was 17.3 cm. Two of 63 patients (3%) had pelvic lymph node metastasis where none of the 24 patients had para-aortic lymph node metastasis. From the histological review, 31 patients had microinvasive peritoneal implants and 16 had non-invasive peritoneal implants.

Oncologic outcomes are shown in Table 3.

Characteristics	Number of patients (%) or Median (Range)*
Follow-up time (months)	25.4 (9.9-56.3)
Alive	156 (96)
Recurrence	9 (5.5)
Recurrence with borderline tumor	7 (4.3)
Recurrence with invasive carcinoma	2 (1.2)

Died related to ovarian tumor	1 (0.6)
Died from other causes	6 (3.7)
5-year progression-free survival (%)	93.2 (83.7-97.2)
5-year overall survival (%)	97.4 (92.1-99.2)

Table 3. Oncological Outcomes of Borderline Ovarian Tumor Patients (N=161*).

*7 patients were lost to follow-up

During the median follow-up time of 25.4 months, only 9 patients (5.5%) developed disease recurrence with an estimated 5-year progression-free survival (PFS) of 93.2%. Among these recurrences, 6 and 3 patients had prior stage I and stage II –III, respectively. Of the 9 patients with recurrences, 4 were serous and mucinous types each, the other 1 was endometrioid type. 8 patients had single site recurrence and 1 had recurrence at multiple sites. Among 9 patients with recurrences, 6 were treated by conservative surgical excision, while the remaining 3 underwent definitive surgery. Bilateral BOT was found in 3 patients and only 1 underwent lymphadenectomy. Two patients developed invasive tumor recurrence. One with pelvic lymph node recurrence of endometrioid adenocarcinoma was treated with surgical excision. The remaining 1 with supraclavicular lymph node recurrence of serous adenocarcinoma was treated with chemotherapy.

Five-year overall survival of the 168 BOT patients was 97.4% with 7 deaths. One patient with invasive endometrioid adenocarcinoma recurrence had tumor invasion at rectum and ureters causing severe hemorrhage and renal insufficiency. Five patients died from other underlying diseases and the remaining 1 died from cholangiocarcinoma occurring 6 years after the detection of BOT.

Prognostic factors were analyzed using the univariate and multivariate analyses as shown in Table 4.

Variables		5-Year Progression-Free Survival		
	Univariable		Multivariable	
	HR (95%CI)	p-value	aHR (95%CI)	p-value
Cell type		0.48		
Mucinous	1			
Endometrioid	5.93 (0.54-65.53)			
Serous	3.09 (0.43-21.97)			
Mixed	0.00 (Not report)			
Tumor size (cm.)		0.03		0.04
> 10	1		1	
≤ 10	7.67 (1.28-46.06)		9.68 (1.17-80.25)	
Stage		0.02		0.01
I	1		1	
II-III	8.09 (1.35-48.51)		21.17 (2.04-219.75)	
Primary treatment		0.03		
Definitive surgery	1			
Conservative surgery	11.08 (1.24-99.43)			
Pelvic lymphadenectomy		0.38		
No	1			
Yes	0.38 (0.04-3.37)			
Hysterectomy		0.03		0.03
No	1		1	

Yes	0.09 (0.01-0.77)		0.07 (0.01-0.74)	
Microinvasion		0.95		
No	1			
Yes	0.93 (0.1-8.3)			
Noninvasive implant		0.63		
No	1			
Yes	1.71 (0.19-15.3)			
Laterality		0.07		
Unilateral	1			
Bilateral	5.33 (0.89-31.9)			

Table 4. Univariable and Multivariable Analyses of 5-Year Progression-Free Survival.

HR, hazard ratio; aHR, adjusted hazard ratio, adjusted for tumor size and hysterectomy. Variable selection was considered by forward method with $p \leq 0.10$

In univariate analysis, PFS was significantly worse in patients with advanced stage (P = 0.02), tumor size ≤ 10 cm (p = 0.03), conservative surgery (p = 0.03), and bilateral tumors (p = 0.07). Interestingly, hysterectomy was a protective factor with a hazard ratio (HR) of 0.09 (95% CI 0.01 – 0.77, p = 0.03). Cell types, pelvic lymphadenectomy, micro-invasion, and non-invasive peritoneal implants were not significantly associated with survival outcomes. In multivariate analysis, early stage, tumor size > 10 cm, and hysterectomy were significantly associated with better survival.

Discussion

This study showed that patients with BOT had an excellent prognosis. More than 90% of the patients were detected in the early stage similar to the previous report [11]. The most common cell subtype was mucinous accounting for 70% in our study resembling many studies in East Asia [12-14]. In contrast, serous BOT was more commonly found in North America, Europe, and Middle East. The precise cause of the differences in the histologic distribution in each region remains elusive [15].

Concerning the oncological outcomes, the 5-year PFS of BOT patients in our study was relatively high at 93.2% with 1.2% progression rate to invasive cancer. The previous study reported an approximately 2-3% progression rate [16]. With the low recurrence rate of BOT in this study (5.3%), univariate and multivariate analyses were carried out and showed that advanced stage, tumor size > 10 cm and not performing hysterectomy were significantly associated with adverse survival outcomes. However, generalizability of these findings may not be applicable. In previous study, the significant prognostic factors were advanced stage, age older than 65 years, and the presence of micro-invasion. In univariate and multivariate analyses, hysterectomy was found to be a significant protective factor for recurrence [14]. This may be due to performing bilateral salpingo-oophorectomy [17]. In a case that does not require fertility, hysterectomy should be considered as a standard of treatment.

Many studies reported an increase of recurrence by conservative surgery, especially ovarian cystectomy [6, 18, 19]. In a meta-analysis, the recurrence rates were frequently noted in patients undergoing ovarian cystectomy, bilateral ovarian cystectomy, unilateral salpingo-oophorectomy (SO), and unilateral SO with contralateral cystectomy accounting for approximately 25.3%, 25.6%, 12.5%, and 26.1%, respectively. The better outcomes in patients treated with unilateral SO was observed when compared to those treated with ovarian cystectomy (odds ratio for recurrence reduction = 2.200, 95% CI = 0.793-2.841, p < 0.0001) [20]. However, some

studies reported the safety of using conservative surgery [21, 22]. In our study, conservative

surgery was one of the risk factors for recurrence in univariate analysis but was not significant in multivariate analysis. Therefore, conservative surgery could be offered in selected cases in whom the risk should be informed to the patients and long-term follow-up is required to detect tumor recurrence [23, 24].

BOT tends to have a relatively large tumor size. The average size of mucinous tumors was approximately 13.0-14.9 cm larger than that of serous tumors which were 7.2-7.5 cm [25]. The mean tumor size of BOT in our study was 17.3 cm. Tumor size of larger than 10 cm was significantly associated with a lower recurrence rate regardless of cell type. Previous study by Chen et al., (2017) reported that a tumor diameter larger than 10 cm had better PFS (HR 0.26, 95% CI 0.09-0.70). The strong evidence explaining this correlation remains unknown. Accordingly, patients with larger BOT do not always experience worse oncological outcomes. Therefore, conservative surgery can be offered to younger patients with large tumor size.

The recurrences of BOT in our study were mostly found in patients with advanced stage similar to the previous study [26]. However, the stage of BOT did not significantly affect survival in one study [27]. The existence of non-invasive implantation and micro-invasion did not increase the risk of recurrence [28, 29]. However, these histologic factors could be controversial for surgeons on oncological outcomes and the selection of extension of surgery, especially micro-invasion. Although, many studies illustrated that micro-invasion increased the risk of recurrence, it did not affect survival outcomes and can be successfully treated by the second operation [30]. Pelvic lymphadenectomy was performed in 37% of our BOT patients and 3% had lymph node metastasis. Pelvic lymphadenectomy did not affect the recurrence in univariate analysis. This operation is no longer needed in surgical treatment for BOT [5].

The strength of this study was that all cases were treated in a single institute and the specimens were pathologically reviewed by expert gynecologic pathologists. However, some limitations other than the retrospective nature exist including the short median follow-up time at 25.3 months and a variety of surgical procedures for patients with BOT. Many patients attended later follow-up at other hospitals near home due to public health policy. Therefore, long-term survival outcomes could not be evaluated. The role of tumor marker as preoperative diagnostic methods and adjuvant chemotherapy in BOT remain controversial. These issues were not focused on this research and further study is required to evaluate the precise outcomes.

In conclusion, patients with BOT had an excellent survival outcome. Tumor size larger than 10 cm, early-stage disease, and hysterectomy were significant prognostic factors for better survival. Conservative surgery should be offered to patients who desire to preserve future fertility and long-term follow-up is needed to assure recurrence - free.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Author Contributions

SP, CT and JS contributed to the literature search, study concepts, study design and data collection.

SP, JS, KC and TM contributed to the data analysis and interpretation of data. SP, JS, PS and CT contributed to the drafting of the manuscript. All authors contributed to reviewing and approval of the final version of the manuscript.

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