Prognostic factors predicting recurrence in borderline ovarian tumors

Tzu-I Wu [a], Chyi-Long Lee [a], Meng-Yu Wu [b], Swei Hsueh [c], Kuan-Gen Huang [a], Chi-Ju Yeh [c], Chyong-Huey Lai [a,*]

[a] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 5 Fu-Shin St. Kueishan, Taoyuan 333, Taiwan
[b] Department of Cardiac Surgery, Chang Gung Memorial Hospital and Graduate Institutes of Medical Mechatronics, Chang Gung University, Taoyuan, Taiwan
[c] Department of Pathology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan

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ABSTRACT

Objective. We aimed to investigate outcome of borderline ovarian tumors (BOTs) with respect to methods and extent of surgical approach and to evaluate prognostic factors.

Methods. A retrospective study included consecutive patients with BOT treated from 1984 to 2008. These cases were confirmed by histological review. The influence of clinico-pathological characteristics upon recurrence and death were analyzed by independent sample *t* test, Chi-square test, logistic regression model, and Cox proportional hazard model.

Results. A total of 233 patients were enrolled, 214 in Stage I, 11 Stage II and 8 Stage III. There were 21 relapses, only 5 of which died of disease. 5-year and 10-year overall survival were 97.6% and 96.4%, and recurrence-free survival rates (RFS) were 92.7% and 88.2%, respectively. Median follow-up time for survivors was 81 (range, 0.5–295) months. Median time to recurrence was 31 (range, 5.5–181) months. In multivariate analysis, Stage II/III, cystectomy and higher pretreatment serum CA-125 level ($\geq$ 144 U/mL) were selected for a model predicting 5-year RFS, where risk factor = 0, 1, and 2–3 had odds ratios of 1, 14.9, and 113.3, respectively ($p < 0.001$). Replacing stage with peritoneal implants, the latter two factors along with invasive peritoneal implants were selected. Of the 5 cases died of disease, all had invasive recurrences. Initial laparoscopic or laparotomy approach had no influence on prognosis.

Conclusions. Although BOT has an excellent prognosis, they are not exempted from a risk of recurrence. Stage II/III (or invasive implants), cystectomy and higher pre-operative serum CA-125 were independent variables predicting recurrence.

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Introduction

Borderline ovarian tumors (BOTs) account for 15% of all ovarian epithelial cancers, and 81% of BOTs belongs to Stages I–II according to the 6th annual report of International Federation of Gynecology and Obstetrics [FIGO]. The 5-year overall survival (OS) rate is 87.3% in BOT in 1999–2001 [1]. BOT had been described to have a distinctive pathological morphologic features and much better prognosis compared with frankly invasive ovarian malignancies in the same stage in many studies [1–3]. Over the previous decades, pathologist characterized them as proliferating ovarian tumors with cell stratification, various degree of mitotic figures, nuclear atypia, desmoplastic reaction, absence or presence of intraepithelial carcinoma or micro-invasion, but without obvious stromal invasion [4–6].

Fifteen to 40% of BOTs are associated with peritoneal implants. Invasive peritoneal implants are thought to have direct adverse influence toward relapse and survival [7–11]. However studies have indicated that tumors with non-invasive implants also resulted in 30% of relapse rate or progressive disease [12]. Nevertheless, controversies still exist regarding recurrence-free survival (RFS) and recurrent pattern. In spite of the indolent nature of BOT, they still cannot be exempted from a risk of borderline or frankly invasive relapse.

The primary treatment of BOT is surgery, and adjuvant chemotherapy may be used in some cases with risk factors for relapse or progression. According to the clinical practical guidelines in the world, the standard management of BOT is to perform a complete comprehensive staging when fertility preservation is no longer considered. Given that the childbearing is taken into account, complete staging with preservation of uterus and at least part of one ovary is advised [13–16]. Although the appropriateness of laparoscopic approach for management of frankly-malignant adnexal diseases is still controversial, in previous studies on BOT it seemed relatively acceptable [17–21].

The aim of our study was to investigate the outcome of BOTs with respect to methods and extent of surgical approaches and to evaluate prognostic factors in the patients with BOT.

* Corresponding author. Fax: +886 3 328 8252.
 E-mail address: sh46erry@ms6.hinet.net (C.-H. Lai).

Materials and methods

From January 1984 to May 2008, we conducted a retrospective review, in which 233 patients with BOT were retrieved through a search of the disease code database (International Classification of Diseases of Oncology) and Systematized Nomenclature of Medicine code in Chang Gung Memorial Hospital and were confirmed by pathologic review. The histological typing was performed essentially according to World Health Organization system.

Variables including age, tumor size, Stage, histologic subtype, initial surgical access, excision type, bilateral ovarian involvement, fertility preservation, peritoneal implants, borderline/invasive recurrence and pre-operative serum CA-125 level were collected for analysis. Flow cytometric DNA analysis was performed in 21 patients with relapse as described previously [11]. Complete staging was defined by including lymphadenectomy, infracolic omentectomy and peritoneal biopsy. Those with fertility-preserving surgery and lymphadenectomy were designated conservative staging; otherwise those with hysterectomy and bilateral salpingo-oophorectomy (SO) with complete staging were defined to be radical staging. This case series study was permitted by the Institutional Review Board.

The data were analyzed using the SPSS version 15.0 statistical package (SPSS Inc, Chicago, IL). Spearmen correlation was used to evaluate the association between covariates. Receiver operating characteristics curve analysis was used to determine cut-off points of the continuous variables (such as age, CA125 serum levels). Survival curves were plotted with the Kaplan–Meier method and tested using the log-rank test. Multivariate analyses by the Cox proportional hazard model (Wald stepwise backward regression) was utilized for those covariates selected in univariate analyses. Multivariate logistic regression was used to identify the significant risk factors for recurrence and their coefficients (β). The recurrence-predicting model was developed based on the combination of coefficients of significant risk factors. Their multivariate-adjusted Odds ratios (ORs) and 95% confidence intervals (CIs) were expressed. A p value of < 0.05 was considered statistically significant.

Results

Clinical characteristics

Two hundred and thirty three patients with BOT were retrieved for this retrospective case series study. Thirty-nine (16.7%) cases were treated by laparoscopy approach, and 194 (83.3%) by laparotomy initially. Among those BOTs, 214 (91.8%) patients were Stage I, 11 (4.7%) Stage II, and 8 (3.4%) Stage III. Of 233 cases, twenty-five (10.7%) received cystectomy, and the others (89.3%) got a SO. Seventy-two (30.9%) of 233 cases underwent complete staging, and 145 (62.2%) of 233 patients received fertility-sparing surgery to preserve uterus and unilateral/bilateral ovaries (Table 1). Twenty-six percent (16/61) of serous BOTs involved bilateral ovaries, but only 1.9% (3/157) of mucinous BOTs disclosed bilateral ovarian involvement.

Outcome

Five-year and 10-year OS were 97.6% and 96.4%, and RFS were 92.7% and 88.2%, respectively. Median (range) follow-up time for survivors was 81 (0.5–295) months, and the median (range) time for recurrence is 31 (5.5–181) months. Of the 21 patients who encountered recurrences, seven cases developed invasive recurrent carcinoma, and the other 14 revealed recurrent borderline tumor or implants (Table 2). Among 7 recurrences with invasive carcinoma, five cases died of disease (Patient 1, 13, 15, 16, and

17) and 2 are alive with disease. Other 6 with ipsilateral ovarian borderline recurrences, 7 with contralateral ovarian borderline recurrences, and one with non-invasive implants in pouch of Douglas (Patient 8) were all alive without disease after salvage therapy. All those who died of disease were ≥ Stage II except one (Patient 1) with IC mucinous BOT of DNA index 1.33 and an invasive relapse (Table 2).

Univariate and multivariate analysis of prognostic factors

In univariate analysis, Stage II/III, bilateral ovarian involvement, peritoneal implants, microinvasion in the ovarian tumor and invasive recurrences were associated with poor OS. Stage II/III, cystectomy, bilateral ovarian involvement, non-mucinous BOT, complete surgical staging, peritoneal implants and higher serum CA-125 were poor prognostic factors in 5-year RFS. However, there is no significant difference in RFS or OS between initial laparoscopy and laparotomy access, or between fertility-sparing and non-sparing surgery (Table 3). There were strong correlations between LPS and smaller tumor size and between LPS and cystectomy ($p < 0.001$). Although initial access revealed marginally significant ($p = 0.068$) in RFS by univariate analysis, the multivariate analysis didn't show the same result after adjusting confounding covariates.

Table 1
General characteristics of the study population ($N = 233$).

Characteristic	Total	
	N	(%)
Age (years)	Mean, 41.5 ± 16.8	
	Median, 40	
	Range, 14–100	
Tumor size (cm)	Mean, 17.5 ± 9.4	
	Median, 15	
	Range, 2–50	
Stage	233	
I	214	91.8
II	11	4.7
III	8	3.4
Histologic type	233	
Mucinous	157	67.4
Serous	61	26.2
Mixed mucinous and serous	11	4.7
Endometrioid	3	1.3
Clear	1	0.4
Frozen section	233	
Not done	35	18.7
Performed, benign	40	21.4
Performed, borderline	143	76.5
Performed, malignant	4	2.1
Missing	11	
Surgical access	233	
Laparoscopy	39	16.7
Laparotomy	194	83.3
Excisional type	233	
Cystectomy	25	10.7
Adnexectomy	208	89.3
Bilateral ovarian involvement	233	
No	209	89.7
Yes	24	10.3
Complete surgical staging	233	
No	161	69.1
Yes	72	30.9
Fertility preservation	233	
No	88	37.8
Yes	145	62.2
Adjuvant chemotherapy	233	
No	209	89.7
Yes	21	9.0
Missing	3	1.3
CA-125 (U/mL)	Mean, 204.6 ± 1181.73	
	Median, 39.4	
	Range, 2.8–15,280	