Survival Analysis and Prognosis for Patients with Serous and Mucinous Borderline Ovarian Tumors: 14-Year Experience from a Tertiary Center in Iran

Katayoun Ziari, Ebrahim Soleymani, and Kamyab Alizadeh

Department of Pathology, Be'sat Hospital, AJA University of Medical Sciences, Tehran, Iran

Received: 21 Sep. 2013; Accepted: 8 Aug. 2014

Abstract- The aim of this study was to determine the prognosis and survival for patients with borderline ovarian tumor (BOT). A retrospective review of 30 patients with serous and mucinous BOT treated at or referred to our institution was performed. Fifteen patients (50%) had serous, and the others had mucinous BOT. About 86% of all patients in both groups were in stage I of the disease. The recurrent disease occurred in 7% and 21% of serous and mucinous tumors, respectively. All recurrences, except one in mucinous tumors, were found in advance stage disease. After a mean of 37 and 52 months follow-up, the overall survival was 100% and 93%, and disease-free survival was 93% and 79% for serous and mucinous tumors, respectively. In this series, advanced stage was associated with poor prognosis. However, to obtain more accurate information further studies with number of patients and longer follow-up is recommended.

Acta Medica Iranica, 2015;53(4):199-203.

Keywords: Ovarian neoplasms; Neoplasms; Cystic; Mucinous; Serous prognosis; Survival

Introduction

Epithelial ovarian tumors account for two-third of all primary ovarian tumors. Borderline (low malignant potential) ovarian tumors (BOTs) comprise 10- 20 percent of the ovarian epithelial tumors (1,2). It was initially reported by Taylor in 1929, and was accepted as a separated category by the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) in the first 1970s (2-4). It is reported that borderline ovarian tumors have a higher proliferative activity than benign neoplasms but have no stromal invasion (5).

The most frequent histological subtypes of borderline lesions are serous (two-thirds to three-quarters of these tumors) and mucinous tumors, followed by rare subtypes such as endometrioid, Brenner, and clear-cell tumors (<5%) (1). There is some evidence that borderline tumors may progress to malignancy (6). Thus, despite the good prognosis in the majority of these tumors, they are not quite similar to benign types of ovarian tumors and the concept of the potential of borderline tumors for malignancy should be considered.

Several studies have reported that BOTs are a heterogeneous group of lesions and the mix of various subtypes in a unique classification may blur the actual properties of these tumors. This was one of the moot points in Borderline Ovarian Tumor Workshop held in August 2003 in Bethesda (3,4). Histological studies on these heterogeneous tumors indicate that the pattern of lesions such as BOT with stromal microinvasion, BOT with intraepithelial (noninvasive) carcinoma, or BOT with micropapillary/cribriform pattern greater than five mm have different effects on prognosis and stage of the disease, so that differentiation of the subgroups may be important (4,7,8).

For borderline tumors, the term "implant" rather than "metastasis" is applied to extra-ovarian lesions because the prognosis for patients with advanced-stage borderline tumors is significantly better than those with typical advanced-stage carcinoma. Also, implants were histologically subclassified as "invasive" or "noninvasive" for more accurate prediction of prognosis (9). This study aimed to determine the prognosis and survival of patients with serous and mucinous BOTs in a tertiary center in Iran.

Corresponding Author: E. Soleymani
Department of Pathology, Be'sat Hospital, AJA University of Medical Sciences, Tehran, Iran
Tel: +98 21 39954041, Fax: +98 21 77752281, E-mail address: esoleymani@yahoo.com

Materials and Methods

This retrospective review was performed in patients with BOT treated at, or referred to, Mirza-Kouchak-khan Gynecology Hospital in Tehran, during 1993-2007. The protocol of the study was approved by the Institutional Ethical Committee on Human Research of Tehran University of Medical Sciences. The surgical pathology files of the hospital were searched for all cases of ovarian tumors diagnosed as borderline tumor. After extracting data from BOT patients, the clinical records and pathology slides were reviewed by two experienced and independent pathologists to confirm the primary diagnosis.

The histologic type was established by review of hematoxylin eosin-stained slides, essentially as recommended by FIGO. The following histologic criteria were used to identify borderline tumors: 1) stratification of the epithelial lining of the papillae, with microscopic papillary projections or tufts arising from the epithelial lining of the papillae; 2) nuclear atypia; 3) mitotic activity; 4) intracystic clusters of free-floating cells; and 5) absence of stromal invasion. Mitotic index (number of mitotic figures per 10 high-power fields) was also evaluated.

Based on the histologic features, tumors were classified as 1) atypical proliferative (borderline); 2) BOT with intraepithelial carcinoma; 3) BOT with micro invasive carcinoma; and 4) BOT with micropapillary/cribriform pattern.

Clinical and follow-up information was obtained from the hospital charts, and telephone contacts with patients or gynecologic oncologists. Patients with incomplete follow-up information were excluded from further analysis.

For the statistical analysis, the rate of recurrence as well as the survival status was calculated. The following characteristics were studied: histologic features, stage, and type of surgery. Overall and disease-free survival rates were determined using the Kaplan–Meier method.

Results

A total of 30 serous/mucinous borderline tumors (15 serous BOTs and 15 mucinous BOTs) were reviewed and were the subject of this analysis. Typical BOTs were observed in 6 (40%) and 4 (26.6%) cases in serous and mucinous tumors, respectively. Among mucinous tumors, 9 women (60%) had intestinal type, and 6 (40%) had endocervical-like mucinous BOT. The mean age of patients with serous and mucinous histology was 35 (range: 16-68) years and 29.4 (range: 13-69) years, respectively. The most common clinical presentation was abdominal pain associated with abdominal distention in 33.3% of serous tumor patients or associated with a pelvic mass occurring in 28.6% of patients with mucinous tumor. The most common associated gynecologic finding was endometriosis (three patients) or leiomyoma (three patients). Peritoneal endosalpingiosis was identified in one patient with mucinous BOT. The mean tumor size was 8.5 (range: 5-19) cm and 16 (range: 7-30) cm in serous and mucinous tumors, respectively. Five serous tumors were bilateral (33% of serous group). A mean of 11 and 14 sections was examined per serous and mucinous tumors, respectively (Table 1).

Table 1. Characteristics and pathologic features of 30 ovarian serous/mucinous borderline tumors

	Diagnosis	No. (%) of cases	Mean age, years (range)	Mean size, cm (range)	Mean no. of sections examined	No. (%) bilateral
Serous	**Atypical proliferative**	6 (40%)	33.8 (16-67)	8 (5-14)	9 (6-11)	1 (16.7%)
	Intraepithelial carcinoma	3 (20%)	33 (24-43)	8 (8)	15 (7-30)	2 (66.7%)
	Micropapillary/cribriform	4 (26.7%)	30.7 (22-44)	7.7 (5-14)	9 (6-17)	2 (50%)
	Microinvasive carcinoma	2 (13.3%)	49.5 (31-68)	12 (5-19)	14 (6-22)	-
	Total cases	15 (100%)	35 (16-68)	8.5 (5-19)	11 (6-30)	5 (33%)
Mucinous	**Atypical proliferative**	4 (26.6%)	20.5 (13-31)	13.5 (10-16)	12 (7-15)	-
	Intraepithelial carcinoma	6 (40%)	28.5 (18-38)	20.5 (10-30)	14 (5-20)	-
	Micropapillary/cribriform	4 (26.7%)	20.5 (15-28)	20 (15-27)	19 (18-21)	-
	Microinvasive carcinoma	7 (46.7%)	35 (18-69)	16.5 (7-27)	17 (7-26)	-
	Total cases	15 (100%)	29.4 (13-69)	16 (7-30)	14 (5-26)	-

Of the 30 patients with available staging information, 26 were at the stage I (87%). Four patients (in serous BOTs) had a complete staging procedure (including peritoneal washing, multiple biopsies, and omentectomy), 13 [5S (serous)+8M (mucinous)] had a partial staging procedure (including peritoneal washing, omental and/or peritoneal biopsy), and 13 (6S+7M) had surgical exploration of the peritoneal cavity without formal staging.

Treatment information was also available for 30

patients. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed in 12 (7S+5M) patients (with or without chemotherapy), cystectomy with unilateral salpingooophorectomy in 18 (8S+10M) patients. A platinum-based chemotherapy was performed for 5 (2S+3M) patients.

Mean follow-up time was 37.1 (range: 7-81) months and 52.5 (range 21-82) months in serous and mucinous BOTs, respectively. Among patients with stage I, all in serous BOT (13 cases) and 11 of 12 cases in mucinous BOT were alive with no evidence of disease. One of the 12 patients with stage I of mucinous BOTs was alive with disease. Of the five patients with advanced-stage tumors, one with serous BOT was alive with no evidence of disease, 2 (1S+1M) were alive with disease, one with mucinous BOT died of disease, and one in mucinous group was lost to follow-up.

Four patients had recurrent disease at 14, 23, 29, and 37 months follow-up, respectively. Of them three (1S+2M) were alive with no evidence of disease at follow up (79-82 months after initial diagnosis) and one who had mucinous BOT with recurrent at 23rd month, had died 46 months after the diagnosis. The mean overall survival was 37.1 (range: 7-81) months and 52.5 (21-82) months for serous and mucinous BOTs, respectively. The mean disease-free survival was 36 (range: 7-81) months and 47.5 (21-79) months for serous and mucinous BOTs, respectively (Table 2). After a mean of 37.1 months, follow-up in current serous patients, the overall and disease-free survival was 100% and 93.3%, respectively. The overall and disease-free survival in mucinous BOTs after a mean of 52.5 month's follow-up was 92.8% and 78.6%, respectively.

Table 2. Stage and survival data for ovarian serous/mucinous tumors

	Diagnosis	Mean follow-up, months (range)	Stage I		Stage > I	
			No. (%)	Survival data	No. (%)	Survival data
Serous	Atypical proliferative (n=6)	45 (7-81)	6 (100%)	6 NED (100%)	-	-
	Intraepithelial carcinoma (n=3)	17.5 (9-34)	3 (100%)	3 NED (100%)	-	-
	Micropapillary/cribriform (n=4)	26 (13-45)	2 (50%)	2 NED (100%)	2 (50%)	1 NED (50%); 1 AWD (50%)
	Microinvasive carcinoma (n=2)	57.5 (40-75)	2 (100%)	2 NED (100%)	-	-
	Total cases (n=15)	37.1 (7-81)	13 (87%)	13 NED (100%)	2 (13%)	1 NED (50%); 1 AWD (50%)
Mucinous	Atypical proliferative (n=4)	61.5 (21-79)	4 (100%)	4 NED (100%)	-	-
	Intraepithelial carcinoma (n=6)	49.5 (28-79)	6 (100%)	6 NED (100%)	-	-
	Micropapillary/cribriform (n=4)	69 (46-82)	1 (25%)	1 AWD (100%)	3 (75%)	1 DOD (50%); 1 AWD (50%) 1 UN
	Microinvasive carcinoma (n=7)	54.5 (21-82)	7 (100%)	7 NED (100%)	-	-
	Total cases (n=15)	52.5 (21-82)	12 (86%)	11 NED (91.7%); 1 AWD (8.3%)	3 (20%)	1 DOD (50%); 1 AWD (50%) 1 UN

NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; UN, unknown

Discussion

Current study reports 30 serous/mucinous borderline tumors found during 14 years in one of the greatest gynecological referral center in Tehran, Iran. Fifty percent of our patients had serous BOTs.

Serous BOTs are the most common type of borderline tumors, and bilaterality is seen in 25-50% of serous histotypes (10). Studies indicated that serous BOTs are the most common during the fourth and fifth decades of life, with an average patient age of 46 years (11). In this study, the bilateral serous BOT was seen in 30% of serous tumors. The mean age of patients with serous BOT was about 35 years. However, all mucinous BOTs were unilateral, and 60% of them were intestinal type. This is in accordance with the studies on mucinous BOTs which stated that over 90% are unilateral and intestinal type accounts for about 85% of mucinous tumors (12).

In the literature, several prognostic factors are related to serous BOTs and stage of the disease is the first one (13). At the time of presentation, 70% of serous BOTs are at the stage I (14). Current finding showed that 86% of serous BOT patients were diagnosed with stage I. Although, most of the patients with serous BOT have a good prognosis at stage I, some studies have reported early recurrent with high-grade carcinomas (7). However, after a mean of 37 months follow-up in our serous patients, the overall and disease-free survival was 100% and 93.3%, respectively. This is consistent with other currently reported studies (4). The only recurrent disease was seen in advanced stages of serous BOTs that

occurred in one of the two patients with stage III. In addition to the advanced stage seen in this patient, there was necrosis and commonly found mitotic figures (Mitotic index between 5 and 10) in tumor cells. Thus, disease-free survival was influenced by these two factors.

Based on recent data available in the literature, over 80% of patients with mucinous BOT are at the stage I and a 5-year survival rate are up to 99 to 100%. But the mortality may reach up to 50% of patients with advanced stages (14). Similarly, in the present study, overall and disease-free survival in mucinous BOTs at stage I was 100% and 91.7%, respectively. However, both cases with advanced-stage of mucinous BOTs and known follow-up data had recurrence, and one died of disease.

The lower frequency of typical serous BOTs than other serous subtypes compared to other studies may be because of some selection bias, as the included cases in our tertiary care gynecological center may be referred with uncertain or complicated diagnosis problem whereas typical serous BOTs may be easily diagnosed and treated in other centers.

Most histological studies are consistent regarding the higher tendency of micropapillary serous BOTs to bilateral involvement and exophytic growth, as well as association with peritoneal implants and recurrence (3, 4, 9, 15). Similarly, in the present study, out of four patients with micropapillary serous BOT, two had an advanced-stage of the disease, and recurrent disease was seen in one of them 13 months after diagnosis. However, longer follow-up may reveal more women with recurrent disease. Although, similar to this study, in most reports microinvasive pattern of serous BOTs had a good prognosis (3, 16, 17), some did not (15). Our two patients with microinvasive serous BOT had no recurrent disease after 40 and 75 months of follow-up. No mortality was observed in serous BOT with intraepithelial carcinoma; women followed-up for 9 to 34 months. Of course, the length of follow-up may be inadequate for a certain conclusion.

It is important to notice that all mucinous cases with recurrence in our patients showed features of several histologic subtypes; two were composed of micropapillary/cribriform, intraepithelial carcinoma, and microinvasive carcinoma; and one of them was composed of micropapillary/cribriform and microinvasive carcinoma and this is in consistence with other studies (18). In addition, due to the lower age at diagnosis among women who desire to preserve their fertility the conservative surgery was performed. Thus, several factors are important to the selection of treatment strategy in these complicated conditions (4).

Although, low-stage borderline tumors have an excellent prognosis, recurrent or even death may occur in the advanced stages. The effect of FIGO-stage on survival is consensus and the result of this study is compatible with other literatures. However, to obtain more accurate information on the influence of histologic features and treatment procedures on overall and disease-free survival, further studies with number of patients and longer follow-up is recommended.

References

1. Morice P, Uzan C, Fauvet R, et al. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. Lancet Oncol 2012;13(3):e103-15.
2. Trope CG, Kaern J, Davidson B. Borderline ovarian tumours. Best Pract Res Clin Obstet Gynaecol 2012;26(3):325-36.
3. Al-Nafussi A. Ovarianepithelial tumours: common problems in diagnosis. Curr Diagnos Pathol 2004;10(6):473-99.
4. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: Diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. Hum Pathol 2004;35(8):918-33.
5. Bagade P, Edmondson R, Nayar A. Management of borderline ovarian tumours. Obstet Gynaecol 2012;14(2):115-20.
6. Bouchardy C, Fernandez S, Merglen A, et al. Increased risk of second cancer among patients with ovarian borderline tumors. Gynecol Oncol 2008;109(2):210-4.
7. Parker RL, Clement PB, Chercover DJ, et al. Early recurrence of ovarian serous borderline tumor as high-grade carcinoma: a report of two cases. Int J Gynecol Pathol 2004;23(3):265-72.
8. Slomovitz BM, Caputo TA, Gretz HF 3rd et al. A comparative analysis of 57 serous borderline tumors with and without a noninvasive micropapillary component. Am J Surg Pathol 2002;26(5):592-600.
9. Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. Am J Surg Pathol 2001;25(4):419-32.
10. Tinelli R, Tinelli A, Tinelli FG, et al. Conservative surgery for borderline ovarian tumors: a review. Gynecol Oncol 2006;100(1):185-91.
11. Acs G. Serous and mucinous borderline (low malignant

potential) tumors of the ovary. Am J Clin Pathol 2005;123(Suppl):S13-57.
12. Priya C, Kumar S, Kumar L. Borderline ovarian tumours: An update. Indian J Med Paediatr Oncol 2008;29(2):19-27.
13. Morice P, Camatte S, Rey A, et al. Prognostic factors for patients with advanced stage serous borderline tumours of the ovary. Ann Oncol 2003;14(4):592-8.
14. Lalwani N, Shanbhogue AK, Vikram R, et al. Current update on borderline ovarian neoplasms. AJR Am J Roentgenol 2010;194(2):330-6.
15. Longacre TA, McKenney JK, Tazelaar HD, et al. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (> or =5-year) follow-up. Am J Surg Pathol 2005;29(6):707-23.
16. Prat J, De Nictolis M. Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. Am J Surg Pathol 2002;26(9):1111-28.
17. Diebold J, Amann G, Seemüller F, et al. Diagnostic and molecular genetic pathology of serous borderline tumors of the ovary. Curr Diag Pathol 2004;10(4):318-25.
18. Shappell HW, Riopel MA, Smith Sehdev AE, et al. Diagnostic criteria and behavior of ovarian seromucinous (endocervical-type mucinous and mixed cell-type) tumors: atypical proliferative (borderline) tumors, intraepithelial, microinvasive, and invasive carcinomas. Am J Surg Pathol 2002;26(12):1529-41.