Clinical analysis of borderline ovarian tumors

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Summary

Purpose: The goal of this study was to evaluate the incidence and clinical features of borderline ovarian tumors (BOTS). *Methods:* We retrospectively performed chart reviews of 22 patients with BOTS who were diagnosed and treated in the university medical center from 1998 to 2009 inclusively. *Results:* BOTS among ovarian pathology in our hospital were detected in 22 patients (1.79%). The mean age was 50 years, range (20-90). Post surgical FIGO staging was Stage I = 86.4%, and Stage II = 13.6%. The most common histologic subtype was mucinous (59%). Five patients (22.7%) had a unilocular cyst at ultrasonography. Conservative surgery was performed in 31.8%. One patient of them had normal spontaneous delivery after term pregnancy. Two patients had a recurrence. One patient with recurrent disease underwent transformation to invasive cancer and died 35 months after the initial diagnosis. *Conclusion:* Clinicians should warn patients about the early relapse of BOTS and these patients may need careful follow-up due to the possibility of recurrences.

Key words: Borderline ovarian tumors; Conservative surgery; Recurrence.

Introduction

Epithelial ovarian tumors of low malignant potential were first described by Taylor in 1929 as a group of patients with 'semimalignant' or hyperplastic ovarian tumors without histological evidence of stromal invasion but with peritoneal implants [1]. He noted that these patients had a good prognosis (as tumors with histologic features and biological behavior) between benign and frankly malignant epithelial ovarian neoplasms. In 1971, this group of tumors was accepted by the International Federation of Gynecology and Obstetrics (FIGO) as carcinoma of low malignant potential [1], and in 1973 by the World Health Organization (WHO) as borderline tumors [2]. The 2003 WHO classification defined the borderline tumor as more than two of the tumors lacking stromal invasion, with budding, multilayered epithelium, mitotic activity and nuclear atypia [3]. Borderline ovarian tumors (BOTS) account for 14-15% of primary ovarian neoplasms [4]. Histologic types include serous 55% – the most common – mucinous 40%, mixed 2%, endometrioid 2%, clear-cell < 1% and transitional-cell (or Brenner) tumors < 1%. The latter three histological types are very uncommon – 5% [1]. In up to 10-15% of the BOTS isolated tumor cells or small clusters of tumor cells in the stroma can be detected. One or more such groups may be present. If none of these foci exceed 10 mm^2 or 3-5 mm in the largest diameter the lesion is defined as microinvasion [5]. Peritoneal implants were classified into two types as invasive and noninvasive. BOTS are more common in reproductive-age women (mean age 30-50) and have a much better prognosis than invasive tumors. However, they can be present with metastatic disease and can recur. Recurrences can occur as long as ten or 15 years after the primary tumor, and may be in the form of invasive carcinoma. Because of the generally benign behavior of these tumors, their management has become progressively more conservative, allowing women to maintain their fertility. The response to chemotherapy, hormonal therapy, and radiotherapy was poor. The five-year survival for women with Stage I BOTS is about 95% to 97%, but because of late recurrence the ten-year survival is only 70% to 95%. The five-year survival for Stage II-III patients is 65% to 87% [1]. Approximately 80% of patients during diagnosis present with a FIGO Stage I tumor and recurrences are encountered in approximately 10% of all patients. Recurrences can be seen as late as 10-39 years after initial diagnosis, and 0.6% to 19% of patients have recurrence as an invasive carcinoma [6]. In BOTS, pelvic ultrasound and serum tumor marker CA 125 are widely used in diagnosis. Preoperative CA 125 was increased in 56% of patients with a borderline tumor [7]. Carcinoembryonic antigen (CEA) and CA 19-9 for mucinous tumors have been proposed. Preoperative serum CEA and CA 19-9 were increased in 32% and 45% of borderline mucinous tumors, respectively [7]. The purpose of this study was to evaluate frequency of occurrence, diagnosis, treatment, and clinical outcome for 22 patients with ovarian borderline tumors and compare the findings with the recent literature.

Materials and Methods

We retrospectively performed a chart review of 22 patients with ovarian borderline tumors who were diagnosed and treated in one university hospital in Korea from 1998 to 2009 inclusively. The incidence of BOTS among ovarian pathology in our hospital during this period was 1.79%. Histological classification and staging of all tumors were determined according to the 2003 WHO classification and the FIGO classification [3, 7]. All patients underwent primary surgical treatment in order to achieve surgical reduction and to establish the stage of the disease. All patients received intraoperative frozen section. The conservative surgery with staging procedure was performed in

Revised manuscript accepted for publication April 1, 2010

young patients who desired to preserve fertility. All patients had preoperative serum CA 125, CA 19-9 and CEA measured and underwent transvaginal sonography. For CA 125 the upper limit of normal is 35 U/m and the upper limit of normal CEA values is 4.9 ng/ml. For CA 19-9, 37 U/ml was used as the upper limit of normal, being the 97th percentile in healthy women. Adjuvant chemotherapy was needed in patients with advanced Stage I or progression to invasive cancer. Secondary cytoreductive surgery was performed on patients who had a recurrence. In all statistical analyses, a p value of < 0.05 was considered statistically significant. Disease-free and overall survival rates were calculated from the date of surgery to the time of recurrence, last follow-up, or death. Disease-free and overall survival curves for patients were constructed according to the Kaplan-Meier method and statistical differences between the curves were calculated with the log-rank test. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 12.0.

Results

Mean age for all 22 patients at the time of diagnosis was 50 years (range 20-90 years). Median follow-up was 42.8 months (range 15-122 months). Thirteen patients had mucinous tumors (59%), five tumors were serous (23%), three tumors were Brenner (13.5%), and there was one mixed tumor (4.5%). Patients included in the study were in Stage I (19/22; 86.4%) and II (3/22; 13.6%). Two patients had an intraepithelial carcinoma lesion and another two patients had microinvasion (9%). CA 125 levels were elevated in six patients (27.3%), CA 19-9 levels were elevated in four patients (18.2%) and CEA levels were elevated in one patient (4.5%). Preoperative CA 125 was more frequently elevated in patients with serous tumors (2/5; 40%) than mucinous tumors (4/13; 30.8%; $p = 0.575$). Preoperative CA19-9 and CEA were only elevated in patients with mucinous tumors (4/13; 25%; $p = 0.336$ and 1/13; 7.7%; $p = 0.867$). However the difference in elevation of tumor markers between histologic type was not statistically significant. Among the 22 women with borderline tumors, 19 (86.4%) underwent laparotomy and three (13.6%) underwent laparoscopy. The type of surgical procedure undertaken varied widely. Conservative surgery (unilateral salpingo-oophorectomy (USO)) was performed in seven (31.8%) patients with disease apparently confined to the ovary, who were young and wanted to preserve fertility. Eleven (50%) patients received surgical staging procedures, six patients received complete surgical staging including lymphadenectomy, and five received limited surgical staging without lymphadenectomy. The analysis of sonography findings of ovarian borderline tumors correlated with histologic types is done. We observed a higher number of multilocular cysts (84.6%) in patients with mucinous BOT than other histologic types. Five (22.7%) BOTS were unilocular, and 17 (77.3%) were multilocular. Seventeen (77.3%) BOTS showed papillae, and five (22.7%) did not. Many BOTS showed fluid/solid mixed echogenic tumors (68.2%). The percentage of pure solid and pure fluid tumors was 13.6 and 18.2%, respectively. The size of tumors ranged from 2-30 cm (mean 13.5 cm). The mean size of the mucinous tumors (15.6 cm) was the largest compared to other histologic types. However the difference in transvaginal ultrasound (TVS) findings of ovarian borderline tumors correlating with histologic types was not statistically significant. One patient with a mucinous BOT had a normal spontaneous delivery at term pregnancy. Tumor recurrence was recorded in two patients (9.0%) with mucinous tumors. During follow-up one patient died due to recurrent disease, 35 months after the initial diagnosis (4.5%). She underwent recurrence two times, 15 and 25 months after the primary surgery. The secondary recurrence progressed to carcinoma, and her age at the time of primary surgery was 37 years. The initial pathology was endocervical type mucinous BOT with intraepithelial carcinoma. The patient received USO and a staging operation (appendectomy, pelvic lymph node dissection, partial omentectomy) as initial surgical procedures. Another patient survived after recurrence. This 24-year-old patient had a mucinous BOT with intraepithelial carcinoma at the time of initial diagnosis. She showed multiple recurrences of the contralateral ovary, right iliac bone and lung 23 months after primary surgery (USO). She has now been alive for 36 months with subclinical lung and iliac bone lesions after the second surgery (USO and partial omentectomy). The cumulative survival rate was 62%/25 months, 31%/50 months and 23%/75 months. The disease-free survival rate was 57%/25 months, 29%/50 months and 23%/75 months.

Discussion

Borderline ovarian tumors tend to occur in a younger age group than do invasive ovarian tumors, more than half of patients are premenopausal [6, 7]. In our study, the mean age at diagnosis was 50 years. This is as same as the average age in the literature; 86.4% of the patients were FIGO Stage I, and Stage III and IV disease were not encountered. Up to 90% of BOTS were Stage I disease. These patients had a 5-year disease-free survival of almost 100% and an excellent overall prognosis [6]. Generally accepted prognostic factors include the extent of residual disease after primary surgery, FIGO stage, histologic type and age. Stage I, serous type and age less than 40 years are the low-risk group. In this series, the most common histologic type was mucinous (59%) which is in contrast with Makarewicz's report on 114 cases [8]. In Korea, approximately 300 cases of borderline ovarian tumors are diagnosed annually, and the majority are histologically mucinous types (70%) followed by serous types (28%) [9-11]. In our study, each incidence of microinvasion or intraepithelial carcinoma was 9% (2 patients each). All of mucinous borderline intraepithelial carcinomas (BIECa) recurred. BIECa may imply a difference in prognosis even in the absence of stromal invasion [12]. Borderline tumors represent intermediate stages of mucinous tumorigenesis and are sometimes difficult to distinguish from BIECa, which can recur in 6% of cases [13]. Microinvasion has been studied separately in muci-

nous and serous tumors. Most investigators believe that microinvasion, regardless of the histologic subtype of the tumor, does not change the patient's overall prognosis, although only relatively few cases have been studied [6, 14]. Assessment of serum CA 125 at diagnosis and in follow-up of BOTS is recommended in many protocols from different institutes [1]. Preoperative increased serum levels of CA 125 have been reported in patients with borderline tumors. In a comparable study in patients with mucinous borderline ovarian tumors authors found, before surgery, elevated CA 125 levels in 52%, elevated CEA levels in 33%, and elevated CA 19-9 levels in 45% [7]. In our study, CA 125 was more elevated in serous tumors than mucinous tumors and either CA 19-9 or CEA was elevated only in mucinous tumors. The preoperative evaluation of BOTS is becoming more important in premenopausal women when the clinician is faced with the dilemma of avoiding unnecessary surgery while identifying possible ovarian cancer. Several authors have recommended less radical surgery (unilateral oophorectomy or cystectomy) for young patients with unilateral BOT. Ultrasound is actually one of the most important presurgical diagnostic tests in the management of adnexal lesions. One study reported that the majority (67.7%) of BOTS found during sonographic examination are multilocular, have thick septa and are sonolucent or of mixed echogenicity [15]. BOTS with a sonographic appearance of unilocular cysts ranged from 13-17% [16]. The presence of papillae in 63-65% of BOTS has been reported [17]. Mucinous tumors tend to be larger at presentation. In our study, 22.7% of BOTS were unilocular, and 77.3% were multilocular; 77.3% of BOTS showed papillae and 68.2% of BOTS showed fluid/solid mixed echogenic tumor. These findings were similar to those of other recent studies. The treatment of BOTS, as in malignant ovarian diseases, has traditionally been radical surgery (hysterectomy with bilateral salpingo-oophorectomy) so as to reduce the risk of recurrence. However, this treatment has been abandoned in favor of more conservative surgery to preserve subsequent fertility in young patients with BOTS. In our conservative surgery group, two of six patients (33.3%) developed recurrence. All of the recurrent patients had mucinous tumors (2/13:15.4%). One patient died due to progression to carcinoma (1/13:7.7%). The natural history of mucinous borderline tumors is poorly understood. However, in a prospective study of 339 cases of BOTS they observed seven progressions (2.0%) into invasive carcinoma, five in serous tumors (2.4%), and two in mucinous tumors (1.6%) [18]. Also, recurrence of Stage I mucinous BIECa has been reported in only 12 of 226 (5.3%) [13, 19]. Both BOTS and BIECa have excellent prognosis, and conservative surgery is the treatment of choice in these cases. Nonetheless, such patients should be completely staged and the tumor should be extensively sampled to rule out stromal invasion because experience with these tumors is still scarce. Furthermore, mucinous borderline tumors are further resistant to anticancer drugs compared with mucinous carcinoma, which is the same experience as our patients. The potential limitations of our study are that it was a retrospective study with a small number of cases. Thus, we cannot consider any clear recommendations for better diagnosis and management of BOTS.

Conclusion

Large prospective multicenter studies with a large number of patients and studies related to K-ras mutation of mucinous tumors are needed in the near future. However we should remember, BOTS may show atypical behavior as two groups – one with an excellent prognosis of 80-90% with a 10-year survival rate and a second with a much poorer outcome. Mucinous BIECa may result in poor outcomes similar to our cases. In Korea's situation mucinous borderline tumors are prevalent, and especially patients with mucinous BIECa may need a warning about early recurrence and close follow-up for a long time.

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