

A retrospective analysis of borderline ovarian tumors in a Greek University Hospital

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Summary

Purpose: The aim of this retrospective study was to analyze the pathologic and clinical characteristics of borderline ovarian tumors. **Methods/Results:** During the period from January 1993 up to December 2002 we found 93 cases of borderline ovarian tumors. The mean age of patients was 44.3 years (range 28.9-59.7 years); 77.4%, 10.8% and 11.8% of patients had Stage I, II and III, respectively. The histological outcomes revealed 52.7% of serous and 41.9% of mucinous origin; 44.1% underwent radical surgery, whereas 55.9% had unilateral salpingo-oophorectomy or cystectomy. The mean follow-up was 84 ± 22 months. The overall five-year survival was 97.4% and 98% for mucinous and serous tumors, respectively. The survival rate was 100%, 90% and 81.8% in Stages I, II and III, respectively. **Conclusion:** From our results it can be concluded that borderline ovarian tumors have a favorable prognosis even after conservative management.

Key words: Borderline ovarian tumors; Management; Prognosis; Low malignant potential.

Introduction

Borderline ovarian tumors (BOTs) are a puzzling subset of epithelial ovarian tumors. These tumors were first described in 1929 by Taylor [1] as semi-malignant tumors but they were classified by FIGO and WHO in the early 1970s [1]. The WHO definition included tumors lacking stromal invasion, with budding, multilayered epithelium, mitotic activity and nuclear atypia [2]. More than two of the above criteria classified the tumor as borderline or of low malignant potential according to the 2003 WHO classification [3]. BOTs account for 15% of epithelial ovarian carcinomas with the majority diagnosed in early stages and being non aggressive. They usually occur in younger ages (1/3 in women under 40 years) [4]. Factors linked with such tumors are oral contraceptive use, menarche, age at first pregnancy and at first delivery, menstrual history, smoking, and family history of ovarian cancer. BOTs may arise from benign serous cystadenomas but the theories of progression to invasive carcinoma are still controversial. Although these lesions might arise from tumors of different origin, many believe that they could develop into invasive carcinoma after progression to an intermediate lesion called micropapillary serous carcinoma [5]. On the other hand, many believe that borderline tumors are characterized by the high frequency of KRAS and BRAF mutations, whereas p53 is often mutated in high-grade tumors [6-8]. Borderline tumors can be managed by more conservative techniques with a favorable prognosis.

Materials and Methods

This was a retrospective analysis of women diagnosed with BOTs and treated between January 1993 and December 2002 at the 2nd Department of Obstetrics and Gynecology, Medical School, University of Athens, Aretaieion Hospital, Athens, Greece. The necessary data were collected by reviewing patient records or hospital electronic bases and by contacting the physicians and patients regarding the age of diagnosis, stage and histological type of the tumor, treatment, relapse rate and 5-year overall survival. Ethical review approval was achieved by the ethical committee of our hospital. Disease staging and tumor characteristics were carried out according to the FIGO criteria.

Results

Ninety-three patients were included in the study. The mean age was 44.3 years (range 28.9-59.7 years). Preoperatively CA125 and CA19-9 measurements were performed in all patients and were positive in 61 (65.6%) and 22 (23.7%) women, respectively; 72 (77.4%), ten (10.8%) and 11 (11.8%) patients had Stage I, II and III disease, respectively. The histological outcomes revealed 49 (52.7%) serous, 39 (41.9%) mucinous, one (1.1%) endometrioid, one (1.1%) Brenner and three (3.2%) of clear cell origin. Eighteen (36.7%) serous tumors were bilateral, whereas 19 (38.7%) revealed extra-ovarian lesions (implants). The majority of the patients (86/92.5%) were treated with exploratory laparotomy whereas seven (7.5%) underwent laparoscopic surgery. Forty-one (44.1%) underwent radical surgery (hysterectomy with bilateral salpingo-oophorectomy), 45 (48.4%) unilateral salpingo-oophorectomy and seven (7.5%) ovarian cystectomy. Omentectomy was performed in 81/93 (87.1%) patients. Appendectomy was performed in all cases in which the frozen section revealed mucinous tumors. Twelve (12.9%) patients were partially staged. It

Revised manuscript accepted for publication August 30, 2007

should be mentioned that 52 (55.9%) women were under 40 years old and had fertility sparing surgery. Twelve (23.1%) women conceived spontaneously and four (7.7%) after IVF use. The mean follow-up was 84 ± 22 months. The relapse rates were one out of 41 (2.5%) in cases of radical surgery, four out of 45 (8.9%) in cases of salpingo-oophorectomy and finally three out of seven (42.9%) in cases of cystectomy. The relapse rate was one out of 19 (5.3%) and seven out of 19 (36.8%), respectively, in cases of non-invasive and invasive implants. Progression into invasive carcinoma was found in three out of 93 cases (3.2%). The type of surgical approach (laparotomy or laparoscopy) did not influence the recurrence rates and/or the survival. The overall five-year survival was 38/39 (97.4%) and 48/49 (98%) for mucinous and serous tumors, respectively. The survival rate was 72/72 (100%), 9/10 (90%) and 9/11 (81.8%) for Stage I, II and III disease, respectively.

Discussion

Our retrospective study revealed similar results to other previous studies on the subject [1, 9, 10]. However, some differences were also found in comparison to such studies.

According to the literature, a preoperative high level of CA125 is usually found in serous tumors (56%), whereas elevation of CA19-9 is usual in mucinous tumors (57%) [9, 10]. According to our findings of CA125 and CA19-9, 65.6% and 23.7%, respectively had positive results. It should also be noted that these values were increased in larger tumors over 8 cm according to the histopathology findings.

The prognostic factors of borderline ovarian tumors are DNA ploidy, stage, histological type and patient age, and also the micropapillary pattern [5, 11, 12]. From our study, it was also shown that invasive implants are a significant risk factor for disease recurrence (36.8% vs 5.3%).

For many years the treatment of borderline tumors was the same as for ovarian carcinomas including peritoneal washing, hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and multiple peritoneal biopsies [13, 14]. Today, the management of such tumors is more conservative. The current management includes peritoneal washing, preferably unilateral salpingo-oophorectomy or cystectomy when the tumor is bilateral; otherwise salpingo-oophorectomy when the history includes, omentectomy, peritoneal biopsies and resection, and appendectomy when frozen section reveals mucinous tumors [1]. Based on the fact that node involvement in Stage I tumors could be found in 0-36% of cases [15] leading to restaging as Stage III, and moreover that the survival rate could reach 98% [16], we did not perform lymph node sampling.

In our cases radical surgery was preferred in older women (> 40 years) whereas conservative techniques were used in younger patients with Stage I tumors according to FIGO or in selected cases with noninvasive

implants. However, it should be noted that cystectomy had a higher risk of intraoperative cyst rupture and recurrence. When fertility-sparing treatment [1, 17] was implemented the need for prolonged and careful follow-up (with clinical examination, CA125 measurements, ultrasound and CT scanning) was essential to prevent recurrences. Careful selection of such candidates is always necessary in these cases. The need for close follow-up is significant but counseling the patient remains difficult as the tumor pathogenesis is still not well understood. Although, a diameter less than 10 cm makes laparoscopic management feasible with fewer complications and shorter hospital stay [18], such treatment was not the rule in our hospital. This was because of the fear of elevated risk of inadequate initial staging, tumor cell contamination, cyst rupture and wound metastasis in comparison to exploratory laparotomy.

The necessity of completing the operation (with removal of the remaining ovary) post pregnancy is still debated. In our patients we preferred to complete the radical treatment when the woman had completed her family planning, except in cases of earlier recurrences. Finally, a study by Zanetta *et al.* [19] showed progression into invasive carcinoma in 2% (7/339 patients), whereas we found an increased percentage (3/93). It should be mentioned that chemotherapy was only used in these three cases of invasive carcinoma and not in borderline tumors.

Taking into account that our study was retrospective, from a single institution, based on patient databases and included only a small number of patients may lead to special limitations of our research. However, we believe that our study could be representative in the understanding of borderline ovarian tumors.

Conclusion

As presented in previous studies, the prognosis of BOTs is excellent with low risk of recurrence even after the use of more conservative management, but there is a need of longer follow-up periods. Fertility-sparing treatment could be performed but careful follow-up is essential. We propose the organization of randomized controlled studies by different oncologic centers in the world which could consequently answer many controversial aspects of ovarian borderline tumors.

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