

A retrospective study of 27 ovarian tumors of low malignant potential

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Summary

Introduction: This study was undertaken to retrospectively review the fertility-sparing surgical treatment and long-term outcome of 27 patients with ovarian tumors of low malignant potential treated at the 1st Department of Obstetrics and Gynecology of Semmelweis University Faculty of Medicine between 1990 and 2000.

Materials and Methods: Between 1990 and 2000, 163 patients with epithelial ovarian tumors were diagnosed and treated. Of these, 27 patients were diagnosed as having low malignant potential (LMP) ovarian tumors. The authors evaluated the effect of histopathologic parameters (histologic type, grade of nuclear atypia, tumor size and tumor growth on the ovarian surface) and clinical parameters (age at diagnosis, stage of disease, and treatment modalities) on prognosis in this group of patients with a long observation time. We reviewed our experience to assess the safety of conservative surgical management of patients younger than age 40 with early stage disease, and to determine the long-term outcome of low malignant potential ovarian tumors.

Medical records were reviewed on all 27 patients to determine age, gravidity, size of tumor, bilaterality, sites of extraovarian involvement, stage of disease and the operative procedure. Follow-up information was obtained from hospital records, and in some cases, by direct patient contact. Statistical comparisons were made by the χ^2 test.

Results: The incidence of LMP tumors in our patient population was 16.5%. The patients ranged in age from 15 to 82 years (median, 45 years). The lesions were staged according to FIGO. The stage distribution was Stage IA in 20 patients, Stage IB in one patient, Stage IC in one patient, Stage IIA in one patient, Stage IIB in one patient, Stage IIC in one patient and Stage IIIA in two patients. The ovarian tumors ranged in size from 3 to 19 cm (median 9 cm) and 15% of the tumors were bilateral. All patients with LMP ovarian tumors were treated with primary surgery; those who were older than 40 (14 patients) were treated with total transabdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO), while patients younger than 40 with early stage disease (12 patients) who wished to retain their fertility potential were treated with fertility-sparing surgery, namely unilateral salpingo-oophorectomy (USO). One patient who was younger than 40 with a Stage IIIA LMP ovarian tumor was also treated with TAH and BSO. Follow-up information was available for all 27 patients with LMP ovarian tumors. Only those patients with a minimum of two years of follow-up were included. Follow-up information from two to ten years (median, 6 years; mean, 6.5 years) revealed that all 27 patients were alive. During the period of follow-up one patient who initially had stage IIIA disease developed recurrent tumor. Fifty percent of patients who underwent conservative fertility-sparing surgical treatment (6/12) subsequently conceived.

Conclusions: This study confirms the excellent prognosis for patients with low malignant potential ovarian tumors. Conservative fertility-saving surgical treatment can be offered to young patients (< 40 years) with early stage (stage I-II) disease who wish to retain their fertility potential. Up to 50% of women in this study who underwent conservative surgery subsequently conceived. The long-term outcome of LMP ovarian tumors is extremely favorable, even when long-term follow-up is extended to ten years.

Key words: Ovarian tumor of low malignant potential; Fertility preservation.

Introduction

Although borderline ovarian tumors were first described in 1929, it has been only about 30 years since this group of tumors was first recognized officially by international sanctioning organizations [1, 2]. In 1973, the World Health Organization (WHO) adopted a classification that included a "borderline" or "carcinoma of low malignant potential" (LMP) group of epithelial tumors [1]. The term "borderline" is felt to be ambiguous and is generally discouraged, although it is occasionally used [3-6]. LMP tumors possess the malignant characteristics of epithelial hyperplasia or stratification, mitotic activity, and cellular and nuclear atypia, but do not have evidence of stromal invasion [3, 5, 7, 8]. LMP tumors represent approximately 10 to 15% of all epithelial ovarian malig-

nancies [1, 5, 9]. In contradistinction to invasive epithelial tumors, most LMP tumors are most commonly confined to the ovaries [10]. Currently, controversy exists regarding the classification of these tumors. Since the prognosis of LMP ovarian tumors is excellent, with 5-years survival rates of almost 100%, some pathologists advocate that this subset should be classified as benign [5, 11]. This concept however met with stiff resistance from the gynecology and pathology communities [12]. The clinical outcome of patients with LMP ovarian tumors remains controversial, especially for those with extraovarian disease [3, 4, 13, 14]. Although the standard treatment for older patients is abdominal hysterectomy and bilateral salpingo-oophorectomy, many young patients who have not completed childbearing can be safely treated with unilateral salpingo-oophorectomy coupled with comprehensive surgical staging [15-17].

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Thus, a clinician is faced with the dilemma of fertility-sparing management versus hysterectomy and bilateral salpingo-oophorectomy in the treatment of ovarian tumors of low malignant potential.

In the past two decades, increasing interest has been directed toward the diagnosis, clinical management, and biologic behavior of ovarian tumors of low malignant potential.

We conducted this retrospective study to review our experience to assess the safety of conservative, fertility-sparing surgical treatment of young patients with early stage disease who desired to keep their fertility potential and to determine the long-term outcome of LMP ovarian tumors.

Material and Methods

Between 1990 and 2000, 163 patients with epithelial ovarian tumors were diagnosed and treated at the 1st Department of Obstetrics and Gynecology of Semmelweis University Faculty of Medicine in Budapest. Of these, 27 patients diagnosed as having low malignant potential (LMP) ovarian tumors represented 16.5% of all cases of ovarian tumors. These 27 patients with LMP ovarian tumors form the basis of this retrospective report. Histopathologic criteria utilized for the diagnosis of low malignant potential have been described by several authors [3, 5, 11, 18]. Tissue was fixed in formaldehyde solution and embedded in paraffin, and histologic typing and grading were performed on hematoxylin and eosin stained slides by one of the authors (N. S.) who did not know the clinical outcome of the patients. The histological preparations were re-evaluated by an experienced gynecologic pathologist (Zs.Cs.). The patients were classified in stages according to FIGO (International Federation of Obstetrics and Gynecology) criteria retrospectively. Initial noninvasive staging procedures included chest radiography and intravenous pyelography. In addition, ultrasonography, barium enemas, pelvic and abdominal computer tomography were done when clinically indicated. Primary laparotomy was done through a vertical incision of sufficient length to allow evaluation of the abdominal contents and the sites at high risk for surface metastases. The tumor capsules were examined for rupture and excrescences. Peritoneal washing and ascites fluid were examined for malignant cells. Pelvic and paraaortic lymphadenectomy, or scraping of the diaphragm were not done routinely. The patients were divided into two subgroups according to age and tumor stage. The first subgroup comprised patients younger than 40 with early stage (Stage I-II) disease. The second subgroup included patients older than 40 regardless of the tumor stage. Surgical treatment was total abdominal hysterectomy and bilateral salpingo-oophorectomy and omentectomy for patients older than 40 (14 patients) and for young patients with advanced tumor (1 patient). Unilateral salpingo-oophorectomy was performed for patients younger than 40 years with early-stage tumor (12 patients). Tumor size was also recorded. The clinical and pathologic records of 27 patients with LMP ovarian tumors were accessed from the hospital archives from 1990 to 2000 and reviewed. The International Federation of Gynecology and Obstetrics (FIGO) staging was retrospectively assigned. Follow-up information was collected from hospital records, and in some cases by direct patient contact. Patients and referring physicians were also contacted via letter or telephone. Statistical analysis was performed using the χ^2 -test; statistical significance was considered as $p < 0.05$.

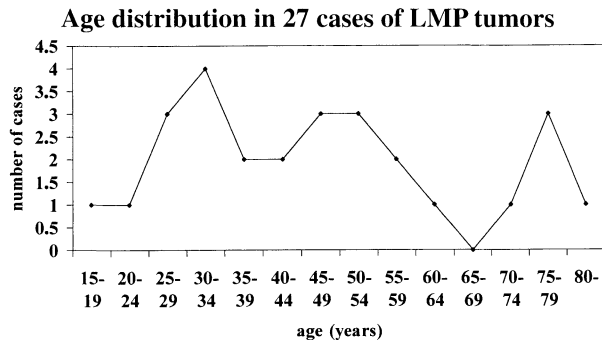


Figure 1.

Results

The incidence of LMP ovarian tumors in our patient population was 16.5%. The patients in this study ranged in age from 15 to 82 years (median, 45 years) (Figure 1). The age distribution at diagnosis shows the highest incidence in the age group 36-40 years (Figure 1). The presenting symptoms are summarized in Table 1. The most common symptoms were increasing girth or abdominal mass and abdominal pain; however, 37% of the patients were asymptomatic.

One patient was pregnant at the time of diagnosis. She was in the second trimester when she underwent conservative surgery consisting of unilateral adnexectomy for Stage IA disease. Subsequently she delivered full-term infant vaginally. The primary ovarian tumors ranged in size from 3 to 19 cm (median, 9 cm) and 15% of the tumors were bilateral. In each instance contralateral ovarian involvement was macroscopically apparent.

The surgical procedures performed at initial laparotomy are shown in Table 2. Fourteen patients who were older than 40 and one patient who was under 40 with a Stage IIIA LMP ovarian tumor underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and omentectomy, while the other 12 patients younger than 40 desiring future fertility with Stage I LMP ovarian tumors underwent unilateral salpingo-oophorectomy and omentectomy.

Table 1. — Presenting symptoms.

Symptoms	Patients	
	N	%
Increasing girth or abdominal mass	7	25.9
Abdominal pain	6	22.2
Abnormal uterine bleeding	2	7.4
Urinary symptoms	1	3.7
Gastrointestinal symptoms	1	3.7
Asymptomatic	10	37.0

Table 2. — Surgical procedures at initial laparotomy.

Symptoms	N	%
TAH and BSO	15	55.5
USO	12	44.4
Omentectomy	27	100.0

Note. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy.

Table 3. — Stage distribution.

FIGO stage	N	%
IA	20	74
IB	1	3.7
IC	1	3.7
IIA	1	3.7
IIB	1	3.7
IIC	1	3.7
IIIA	2	7.4

Table 4. — Histopathologic parameters.

Mean tumor size (range)	9 cm (3-19)
No. of bilaterality	4 (15%)
Tumor rupture	2 (7.4%)
Surface growth	4 (14.8)

The patients were staged retrospectively in accordance with the current FIGO classification (Table 3). Stage distribution was Stage IA in 20 patients, Stage IB in one and Stage IC in one patient (81%).

Stage II in three patients (11%) and Stage III in two patients (8%). Elevated CA-125 was found only in four patients (15%), and 15% of the tumors were bilateral (Table 4). The study patients were followed for two to ten years (median 6 years). Only those patients with a minimum of two years of follow-up were included. All except one patient who initially had Stage IIIA disease were alive without further evidence of disease. The only patient who developed recurrent tumor was 52 years old at the time of diagnosis and she had a Stage IIIA tumor. She was also the only patient who underwent postoperative chemotherapy (6 cycles of cisplatin and cyclophosphamid). The interval from initial surgery to recurrence was 30 months and the site of recurrence was intraperitoneal disease which was confined to the pelvis. She underwent secondary cytoreductive surgery in 1997 and she is still alive without further evidence of recurrence. The other patient who had Stage IIIA disease refused to get postoperative chemotherapy and after being followed for four years she is alive without evidence of recurrence.

Intraoperative rupture of the cyst or the presence of external excrescences in patients with Stage I disease did not appear to confer a poor prognosis. Two patients with Stage I disease had intraoperative rupture of the ovarian cyst and four patients had external excrescences present.

None of these six patients developed recurrence. Because of the desire to preserve fertility, 12 women younger than 40 with early stage (Stage I-II) low malignant potential ovarian tumors were treated with conservative fertility-sparing surgery and six women (50%) have gone on and subsequently conceived to deliver viable infants.

Discussion

Since Taylor's description in 1929 of 'semimalignant' tumors of the ovary, borderline or low malignant potential epithelial ovarian tumors have been recognized as a separate pathological entity [2, 9]. LMP tumors must be recognized since their prognosis and treatment is clearly different from the frankly malignant invasive ovarian carcinoma [9].

A review of 22 series (953 patients) with a mean follow-up of seven years revealed a survival rate of 92% for advanced stage LMP ovarian tumors [12]. Differentiating between LMP ovarian tumors and well-differentiated epithelial ovarian carcinoma solely on light-microscopic criteria may be difficult. There have, however, been considerable discrepancies in the reported incidence of ovarian tumors of low malignant potential. Russel claimed that approximately 25% of all non-benign serous tumors and 75% of all non-benign mucinous tumors were of borderline type [19]. Figures from an annual report show that LMP ovarian tumors account for approximately 17% of all epithelial ovarian malignancies [16]. In our study the LMP group represented 16.5% of all epithelial ovarian tumors.

It is well established that low malignant potential ovarian tumors occur at an earlier age and stage of disease than invasive ovarian carcinoma [9, 12, 15, 16]. The findings in this study concur; the median age of LMP ovarian tumors was 45 years and the stage distribution was 81% Stage I, 11% Stage II and 8% Stage III. In our population the median age of epithelial ovarian carcinoma was significantly older ($p < 0.05$), 59 years, and the stage distribution was 8% in stage I, 5% in stage II, 70% stage III, and 17% stage IV.

Ovarian tumors of low malignant potential tend to exhibit a relatively benign clinical course compared to invasive ovarian carcinoma [9, 12, 15, 16]. Several authors have reported a 5-year survival of 92-97% for all stages, however, recurrences as late as 20 years after initial diagnosis have been reported [9]. Despite the excellent prognosis, survival of patients with LMP ovarian tumors has usually been related to the initial stage of the disease. In the current study, recurrences did not occur in patients with Stage I and II disease, however 50% of patients with Stage III disease (1 out of 2) developed recurrent tumor. This finding confirms that recurrences and survival in patients with tumors of low malignant potential are stage-dependent.

Although extraovarian disease appears to be an important prognostic factor, the pathogenesis of peritoneal, diaphragmatic, omental, and retroperitoneal lymphatic involvement by this tumor is a matter of controversy [12]. The controversy has focused on the issue of whether these tumor implants are metastatic lesions or multifocal proliferation of coelomic mesothelium which has retained Mullerian potential at extraovarian sites [20]. It is difficult to understand the presence of low-grade lesions widely disseminated over the peritoneal cavity [20].

The appropriate therapy for LMP ovarian tumors remains controversial. In early stage disease (Stage I-II) no additional treatment is indicated for a completely resected tumor of low malignant potential [9]. When it is desirable to retain childbearing potential, a unilateral salpingo-oophorectomy can be an adequate therapy. When childbearing is not a consideration, a total abdominal hysterectomy and bilateral salpingo-oophorectomy is appropriate therapy [9]. For patient with more advanced stage disease chemotherapy and/or radiation therapy are not indicated, since there is scant evidence that postope-

rative chemotherapy or radiation therapy alters the course of this disease in any beneficial way, as the recent National Institutes of Health (NIH) Consensus Conference on Ovarian Cancer has concluded [9, 21-24]. These tumors have been treated at the 1st Department of Obstetrics and Gynecology of Semmelweis University Faculty of Medicine up to 1990 according to the same principles as those for invasive epithelial ovarian carcinoma. According to a retrospective study which included 370 LMP ovarian tumors treated at a single institution the 15-year relapse rate was 7%, including all stages, but 3% when considering Stage I disease only [15]. This may indicate that treating all stages of LMP ovarian tumors according to the same principles as those for invasive epithelial ovarian carcinomas may have been overtreatment [25].

With the intention of finding the most harmless, effective, and sufficient treatment for young patients with early ovarian tumors of low malignant potential, we retrospectively studied 27 patients younger than 40 years, who wished to keep their future fertility with Stage I-II LMP ovarian tumors with a median follow-up of six years.

Surgical staging should include careful and thorough inspection and palpation of all mesenteric and peritoneal surfaces as well as the greater and lesser omentum, multiple peritoneal biopsies, which encompass any suspicious areas, and cytologic washings of the abdomen and the pelvis.

For young women with Stage I low malignant potential ovarian tumors who wish to retain ovarian function and whose thorough operative staging and inspection reveals the contralateral ovary to be grossly uninvolved, unilateral oophorectomy seems to be adequate treatment [17]. In our study, there was no recurrence among patients who were treated by fertility sparing surgery. Although wedge resection of the contralateral ovary has been advocated by numerous authors to evaluate the presence of grossly inapparent microscopic borderline tumor, it appears that biopsy of a carefully inspected normal ovary is probably not warranted due to a risk of postoperative infertility, reported to be approximately 14% [12]. We do not feel that salpingo-oophorectomy and hysterectomy are indicated for removal of the residual ovary after fertility is no longer required, although such therapy has been recommended by others [26].

In this study of Stage I-II LMP ovarian tumors, none of the 12 patients in which less extensive surgery was performed relapsed or died of disease during the follow-up period, and half of them subsequently conceived and delivered viable infants. Nevertheless we recommend standard surgery to include omentectomy and peritoneal washing. Our results support the conservative fertility sparing surgical management of young patients with Stage I-II ovarian tumors of low malignant potential who desire future fertility.

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