Ovarian carcinoma of low malignant potential treated at the Jewish General Hospital, Montreal, between 1973 and 1997

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Objective: To review the epidemiologic and pathological characteristics and the management of ovarian cancer of low malignant potential (LMP) at a university teaching institution.

Data source: Hospital charts from 1973 to 1997.

Data extraction: The authors carried out a manual study of the individual hospital charts covering the study period.

Data synthesis: The findings of this review revealed that the mean age of the 30 women in the study was 48.7 years and was similar in the subgroups of women having serous (18) and mucinous (9) types. In those women for whom staging information was available, all had either stage I disease (12 serous, 7 mucinous) or stage III disease (4 serous, 1 mucinous). Treatment consisted of: total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with or without omentectomy (OM); BSO, unilateral oophorectomy or ovarian cystectomy alone; or TAH, OM and left salpingo-oophorectomy in women with stage I tumours. All women with stage III tumours underwent TAH, BSO and OM. The recurrence rate was low. Only 1 of 22 stage I tumours but 3 of 5 stage III tumours recurred.

Conclusions: Appropriate postoperative treatment for women with this type of ovarian cancer should be conservative. However, the management of higher stage disease remains controversial.

Objectif : Examiner les caractéristiques épidémiologiques et pathologiques et la prise en charge du cancer de l'ovaire de faible potentiel malin (FPM) à un établissement d'enseignement universitaire.

Source des données : Dossiers d'hôpital de 1973 à 1997.

Extraction des données : Les auteurs ont réalisé une étude manuelle de chaque dossier d'hôpital portant sur la période d'étude.

Synthèse des données : Les constatations tirées de cette étude ont révélé que les 30 femmes visées par l'étude avaient en moyenne 48,7 ans et que les sous-groupes de femmes atteintes d'un type de cancer séreux (18) et mucineux (9) avaient le même âge moyen. Toutes les femmes pour lesquelles on disposait de renseignements sur la détermination du stade étaient atteintes d'un cancer de stade I (12 séreux, 7 mucineux) ou de stade III (4 séreux, 1 mucineux). Le traitement a consisté à procéder aux interventions suivantes : hystérectomie abdominale totale (HAT) et salpingo-oophorectomie bilatérale (SOB) avec ou sans omentectomie (OM); SOB, oophorectomie unilatérale ou ablation du kyste ovarien seulement; ou HAT, OM et salpingo-oophorectomie gauche chez les femmes qui avaient une tumeur du stade I. Toutes les femmes qui avaient une tumeur du stade III ont subi une HAT, SOB et OM. Le taux de récidive était faible. Seulement une des 22 tumeurs de stade I est réapparue, mais trois des cinq tumeurs de stade III sont réapparues.

Conclusions : Le traitement postopératoire approprié des femmes atteintes de ce type de cancer de l'ovaire devrait être conservateur. La prise en charge de cancers des stades plus avancés continue toutefois de susciter la controverse.

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In 1929, Taylor[1] presented a series of women who had ovarian epithelial tumours that appeared malignant but behaved in a relatively benign manner. He proposed the establishment of a "borderline" category of epithelial ovarian neoplasm. However, his suggestion was not immediately accepted. In 1961, the International Federation of Gynecology and Obstetrics (FIGO) suggested a histologic classification in which epithelial ovarian tumours would be divided into the following: benign neoplasms, carcinomas of low malignant potential (LMP) and tumours with distinctly malignant characteristics. This classification became effective in 1971. Subsequently, LMP ovarian carcinomas were defined by the World Health Organization as tumours that exhibit varying degrees of epithelial proliferation, nuclear abnormalities and mitotic activity but show no evidence of destructive stromal invasion.[2] Such tumours, however, can be associated with peritoneal implants in 30% to 40% of all cases.[3,4] Recent literature favours the term "atypically proliferating surface epithelial-stromal tumours" or "proliferating surface epithelial-stromal tumours" over LMP or borderline ovarian carcinoma owing to the excellent prognosis of this disease compared with malignant ovarian carcinoma.[5–7]

To compare the outcome for patients having LMP ovarian carcinomas seen in the Sir Mortimer B. Davis-Jewish General Hospital (JGH), Montreal, with that reported recently in the literature, we reviewed the hospital charts of all cases of LMP ovarian carcinoma seen at the JGH between 1973 and 1997.

Findings

During the study period, 30 cases of LMP ovarian carcinoma were diagnosed and treated at the JGH. The mean age of the patients at first presentation was 48.7 years (range from 20 to 86 years). For the 18 women who had serous tumour the mean age was 50.4 years, and for the 9 women who had mucinous tumour it was 50.2 years. Two patients had mixed tumours; they were 20 and 36 years old. The last patient had an endometrioid tumour; she was 47 years old. Eight of the 30 (26.7%) women were younger than 35 years at the time of presentation.

Sixteen (53.3%) women were premenopausal and 6 (20%) were nulliparous. None of the patients had a family history of ovarian carcinoma.

Tumour stage

There were no stage II or stage IV tumours at the time of presentation (Table I). In 3 cases (1 mucinous, 2 serous) staging was not available. Four of the 18 (22.2%) patients with serous tumours had stage III disease. Among these 4 patients the peritoneal washings were reported to contain neoplastic cells in 2. In the 2 patients with serous tumours for whom staging was not available, results of peritoneal washings were also not recorded. Tumour had spread beyond the ovaries (stage III) in 1 out of the 9 (11.1%) women with mucinous tumours. In this woman there was associated pseudomyxoma peritoneii which was widespread and diffusely involved the peritoneal surfaces and the bowel.

Treatment

Table II describes the operative procedure done according to the stage of the disease. Of the 5 patients with stage III tumour who underwent initial total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and omentectomy, only 2 had postoperative chemotherapy. Chemotherapy consisted of cyclophosphomide and cis/carbo platinum plus doxorubicin as was recommended in 1973 and in 1985, respectively, by the JGH Tumour Board. The other 3 patients received no further treatment.

Table I

Stage and Histologic Type of Ovarian Tumours According to the International Federation of Gynecology and Obstetrics

	Histologic type, no. (%)				
Stage	Serous	Mucinous	Mixed	Endometrioid	Total
I	12 (66.7)	7 (77.8)	2 (100.0)	1 (100.0)	22 (73.3)
II	—	—	—	—	—
III	4 (22.2)	1 (11.1)	—	—	5 (16.7)
IV	—	—	—	—	—
Unknown	2 (11.1)	1 (11.1)	—	—	3 (10.0)
Total	18 (60.0)	9 (30.0)	2 (6.8)	1 (3.3)	30 (100.0)

Table II

Treatment, by Stage, of 30 Women Having Ovarian Cancer of Low Malignant Potential

Stage	TAH/BSO + OM	TAH/BSO	BSO	UO	OC	TAH/OM/LSO
I	11	1	1	4	4	1
III	5	—	—	—	—	—
Unknown	1	2	—	—	—	—

TAH = total abdominal hysterectomy, BSO = bilateral salpingo-oophorectomy, OM = omentectomy, UO = unilateral oophorectomy, OC = ovarian cystectomy, LSO = left salpingo-oophorectomy.

One 57-year-old woman with stage I disease (serous tumour) was treated with TAH, partial omentectomy and right salpingo-oophorectomy because she had already undergone left salpingo-oophorectomy elsewhere for which the pathological diagnosis was not obtainable.

A 70-year-old woman with stage I disease was treated with BSO and a total colectomy for concurrent right serous LMP ovarian cancer and metastatic colon cancer (she had had a previous TAH).

Seven (88%) of the 8 women who were younger than 35 years at the time of diagnosis had stage I disease. They were treated conservatively by unilateral oophorectomy (4) and ovarian cystectomy (3). The remaining patient in this subgroup had stage III disease and underwent TAH, BSO and omentectomy.

Tumour recurrence

Only 4 (13.1%) of the 30 women had recurrent disease after initial therapy (Table III). Three (60%) of the 5 women with stage III tumour presented with recurrent disease, including the patient with a mucinous LMP ovarian cancer and the 2 patients with stage III serous LMP ovarian cancer who had received chemotherapy postoperatively. Only 1 (4.5%) of the 22 women with stage I disease has had recurrent disease. All of those having recurrent ovarian LMP cancer were still alive at the time of writing.

So far none of the women seen at the JGH have died of their disease. Only 1 patient died, 12 years after her initial treatment for left ovarian mucinous LMP tumour with TAH and BSO, at the age of 85 years of pneumonia and chronic obstructive pulmonary disease. Unfortunately no staging information was recorded on this patient's chart, nor did she undergo an autopsy. The cause of death was listed as respiratory failure.

Discussion

Epithelial ovarian carcinomas of LMP tend to occur in patients at a younger age than malignant ovarian neoplasms. In women younger than 40 years, about 60% to 70% of ovarian neoplasms are of borderline malignant potential, whereas in women older than 40 years, only 10% are of borderline malignancy.[8] In this study, the tumours occurred in a group of women whose mean age was 48.7 years, which is younger than the mean age of patients with malignant ovarian carcinomas.

An LMP form has been described for each histologic type of epithelial ovarian neoplasm. The commonest, however, is epithelial ovarian carcinoma of LMP, which accounts for approximately 15% of all epithelial ovarian malignant tumours.[9] Of these, the serous borderline tumours (approximately 5% to 10% of all malignant serous carcinomas) and the mucinous borderline tumours (approximately 20% of all malignant mucinous tumours) are the most frequent.[10] Also quite common are mixed seromucinous borderline tumours. They are defined as tumours that fulfil the criteria for borderline serous tumours, but in which more than 40% of the cells contain intracytoplasmic mucin.[4]

Ovarian carcinomas of LMP are discovered more frequently at an earlier stage than malignant ovarian neoplasms (about 75% are diagnosed at stage I).[3] This accounts for their much more favourable survival rate and correlates with the findings of this study. Most of our patients (73%) presented at an early stage (stage I).

The traditional approach to borderline ovarian carcinomas unrelated to their histologic type has always been to include careful staging, which consists of inspection of all peritoneal surfaces, cytologic washings of the ab-

Table III

Clinical Details of 4 Patients Having Recurrent Ovarian Tumour of Low Malignant Potental

Patient no.	Age at first treatment, yr	Stage	Histologic type	Initial treatment	Age at recurrence, yr	Treatment of recurrence
1	34	III	Serous	TAH, BSO, PO, CH	39 41	Reoperation: ureteral bypass Reoperation: splenectomy CH — paclitaxel + carboplatinum
2	40	III	Serous	TAH, BSO, PO, CH	64	Reoperation for pelvic mass
3	57	I	Serous	TAH, RSO	65	Reoperation: PO, left retroperitoneal cystectomy + kidney obstruction
4	65	III	Mucinous + pseudomyxoma peritoneii	BSO, PO, appendectomy progesterone	67	TAH Portacath (cytotoxicity)

PO = partial omentectomy, CH = chemotherapy, RSO = right salpingo-oophorectomy.

domen and pelvis, and a sampling of the pelvic and aortic lymph nodes.[8] Recently, the need to do a biopsy of a normal-appearing contralateral ovary and the need for lymph-node biopsy have been questioned.[11,12]

Proper staging of the tumour is of major importance as shown by Massad and colleagues[13] who reviewed the results of 15 papers that contained sufficient information to allow classification. They found that only the stage of the disease proved consistently to be of prognostic importance. Their findings pointed out that most patients have an excellent prognosis with a risk of persistence, recurrence or death of only 4.0%. However, the risk of recurrence or death increases dramatically as the stage of the disease increases, with a 10-fold difference between stage I and stage III/IV disease. In patients with peritoneal involvement, death can occur by progressive intestinal obstruction.

In this study, only 1 (4.5%) of the patients with stage I disease had tumour recurrence. Tumour implants outside the pelvis (FIGO stage III) were present in 16.7% of the women. Among these women the recurrence rate was much higher (60%). Nevertheless, even the patients with recurrent disease seem to have a fairly good prognosis. Our findings match those reported in the recent literature on LMP ovarian cancer.

The appropriate postoperative treatment for patients with high-stage borderline tumour remains controversial. Responses to chemotherapy or radiotherapy have not been established. No efficacy of postoperative therapy could be demonstrated in several retrospective reports[14–17] although others claimed a beneficial effect.[18–20] An aggressive surgical resection seems to give the opportunity for prolonged palliation and long-term survival. Furthermore, the addition of chemotherapeutic agents normally used for the treatment of epithelial ovarian carcinoma seems reasonable, but response rates are not yet established.[21]

A recent study[22] compared the effects of postoperative therapy consisting of a single, orally administered alkylating agent, melphalan, with a complex regimen employing cyclophosphamide, hexamethylmelamine, doxorubicin and cisplatin (CHAD). Women who failed treatment with melphalan were crossed over to treatment with CHAD minus the cyclophosphamide. Response to treatment and clinical complete response rates were higher in women receiving CHAD (60% and 38% respectively), but these differences were confined to women older than 50 years and women suboptimally debulked at the time of initial cytoreductive surgery. The results of this study suggest that platinum-based therapies should be employed as the first postoperative therapy in stage III or IV ovarian LMP tumours. More studies are necessary to compare the prognosis after debulking surgery alone or after additional chemotherapy and radiotherapy.

The findings in the JGH concerning the effect of postoperative chemotherapy correlate with the ones described by Barnhill and colleagues[14] and others.[15–17] Postoperative chemotherapy in these cases did not seem to prevent recurrence for stage III disease, but this result must be looked at very carefully since only 2 patients in our study received this treatment.

Because of the very good prognosis for stage I disease reported by Barnhill and associates[8] and Tazelaar and and colleagues,[23] it seems appropriate that unilateral salpingo-oophorectomy is an adequate therapy for women with a stage I ovarian LMP tumour. This is important because of the younger age of women in whom these tumours are frequently diagnosed and because preservation of fertility is a concern for many of them. Some investigators have concluded that not only unilateral adnexectomy but cystectomy alone may be adequate in borderline tumours confined to a single ovary.[23–25] After careful follow-up, Lim-Tan and associates[26] found no decrease in survival for patients treated with unilateral or bilateral cystectomy alone. A more recent study showed that even laparoscopic procedures in ovarian tumours of borderline malignancy have a similar recurrence rate to laparotomy although there appears to be a higher risk of cyst rupture during the operation.[27] The therapy for postmenopausal women with early stage LMP ovarian cancer should still consist of TAH and BSO as recommended for other ovarian neoplasms in that age group.

As proposed by recent literature,[8,23] younger patients with LMP ovarian tumours should be treated with less invasive operative methods in stage I disease. All of our patients who presented with stage I disease who were younger than 35 years underwent either unilateral salpingo-oophorectomy or ovarian cystectomy. None of these patients has had tumour recurrence. This encourages the practice of more conservative surgery for young patients with stage I LMP ovarian carcinoma who want to preserve their fertility.

The findings and follow-up of the cases of LMP ovarian cancers diagnosed in the JGH between 1973 and 1997 confirm the relatively benign nature of this type of tumour and its excellent prognosis, especially when diagnosed early.

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