

Management of Low Malignant Potential Tumour of the Ovary

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BACKGROUND

The category of low malignant potential tumours of the ovary (LMP) also referred to as borderline tumours of the ovary was introduced in 1971 by the International Federation of Gynecology and Obstetrics (FIGO)¹ when it was recognized that this subset of ovarian tumours has a far better prognosis than epithelial ovarian cancer (EOC). For historic reasons, these tumours are still often confused with EOC, resulting in mismanagement of many patients and the saying, "There is no borderline tumour, just borderline management". Malignant transformation of LMP occurs in fewer than 0.5 percent of cases. This rate is similar to the rate quoted for the malignant transformation of leiomyomata,—0.2 to 0.7 percent—and the latter are not even considered tumours with "low malignant potential".

Low malignant potential tumours are most common in the premenopausal age group. Serous LMP tumours are the most common subtype and they are bilateral in more than 20 percent of cases. The majority present as Stage I. By definition, the staging of LMP tumours is identical to that of EOC.² More recently, an increasing number of publications, including a meta-analysis of 953 serous LMPs, suggest that at least the FIGO Stage I serous LMPs should be viewed as benign

tumours in view of the virtually 100 percent survival rate for patients with this condition.³ This was confirmed in a prospective Gynecologic Oncology Group (GOG) study of 146 patients with 45.7 months mean follow-up.⁴ Non-invasive metastatic implants in LMP tumours do not markedly affect the prognosis and can be viewed as multicentric *in situ* disease. An interesting observation is the strong association of endosalpingiosis (Müllerian inclusion glands) and LMP tumours. There is, unfortunately, a lack of uniform diagnostic criteria for endosalpingiosis, atypical endosalpingiosis, non-invasive implants and invasive implants.⁵

The key to proper clinical management of LMP tumours is an accurate pathological diagnosis distinguishing the LMP tumours from their invasive counterparts and identifying the most aggressive component of LMP tumours. Extensive surgical biopsies serve only the purpose of excluding invasiveness in either the primary tumour or the "metastatic" (multicentric) disease.

Much of the morbidity and mortality associated with LMP tumours is directly associated with the treatment rather than the disease itself.⁵ Malignant transformation is rare and occurred in three of 953³ and one of 76 patients,⁶ respectively, making the incidence less than 0.5 percent overall.

In a retrospective study of 370 LMP tumours with a medi-

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an follow-up of 152.5 months, independent prognostic factors for disease-free and long-term survival were FIGO stage, histological type and patient's age.⁷ Patients with aneuploid tumours had a poorer survival rate than did those with their diploid counterparts. By univariate analysis, the following features influenced survival: histological type (serous); FIGO stage; residual tumour; surgical procedure; tumour growth on the ovarian surface; and pseudo-myxoma peritoneal. Within the 364 tumour-free patients, the extent of surgery and addition of adjuvant treatment had no effect on disease-free survival. Microscopic lymph node metastases do not alter the prognosis.^{8,9}

CLINICAL MANAGEMENT

SURGERY

When the appearance of an ovarian tumour suggests that it may be of low malignant potential and this is reinforced by frozen section, then conservative principles may be followed. Frozen section diagnosis is of limited usefulness due to the often small foci of poor prognostic disease (invasive implants, heterogeneity of mucinous LMP tumours). As a result, there is considerable danger of under-call in a frozen section reported as "LMP-tumour" as the poor prognostic features can easily be missed in this setting. Conversely, an over-call on frozen section may result in unnecessarily radical surgery in patients desiring preservation of fertility. Fertility-sparing procedures (including cystectomy of Stage I LMP tumours) probably do not affect prognosis.¹⁰⁻¹² The staging laparotomy generally should follow the same principles that apply to epithelial ovarian cancer, in particular if laparoscopic surgery is used. Because of the less aggressive nature of LMP tumours and the experience outlined above, the following modifications apply:

1. resect all visible disease;
2. if the omentum is clinically uninvolved, an omental biopsy rather than a total omentectomy is sufficient;
3. if a mucinous LMP tumour is present, an appendectomy should be performed;
4. there is no benefit in resecting clinically normal lymph nodes;
5. there is no benefit in removing clinically uninvolved tissue (e.g. uterus, other ovary);
6. there is no benefit in taking random peritoneal biopsies.

CHEMOTHERAPY

There is no role for postoperative therapy in the treatment of patients with advanced stage LMP tumours unless there are invasive implants or micro-invasive disease in the primary tumour.⁷⁻¹⁶ The few randomized trials in this patient population have failed to show any survival benefit.³⁻²⁰

Given the more aggressive nature of LMP tumours with

invasive implants as well as micro-invasive LMP tumours, chemotherapy could be used (as in low-grade epithelial ovarian cancer). Documentation of chemotherapeutic effectiveness in improving survival has not yet been published, although chemotherapy response to a variety of regimens has been recorded.^{15,17-19}

MANAGEMENT OF RECURRENT DISEASE

Secondary cytoreductive surgery appears to be the only effective treatment for recurrent disease, including recurrences of mucinous borderline tumours of possible appendiceal origin.^{21,22} The sparse experience with chemotherapy in this field does not provide any data to support the use of chemotherapy.

FERTILITY DRUGS, CLOMIPHENE CITRATE AND LOW MALIGNANT POTENTIAL TUMOURS

There is no evidence that the use of clomiphene citrate or other fertility drugs increases the risk of developing LMP tumours. A recent epidemiological analysis of ovarian tumours in infertile women noted the association of clomiphene use and the diagnosis of LMP tumours. In this cohort of 3,837 women, a total of five LMP tumours was discovered.²³ While this and other observations^{24,25} are interesting and deserve further study, it is impossible to tell whether the development of LMP tumours in these women preceded the use of fertility drugs, whether fertility drugs triggered a proliferation of pre-existing LMP tumours, or whether they actually induced transformation of normal epithelial cells into LMP cells.

RECOMMENDATIONS

- Low malignant potential tumours without micro-invasion or invasive metastatic implants have an excellent prognosis regardless of stage. If presenting as FIGO Stage I, they may be considered benign (**Grade B**).
- Restaging of presumably Stage I, LMP tumours is appropriate only if there is strong suspicion of macroscopic residual disease (**Grade B**).
- Such features as micro-invasion, invasive metastatic implants or aneuploidy carry a poor prognosis and these LMP tumours should be treated like low-grade epithelial ovarian cancer (**Grade B**).
- Staging surgery in patients with LMP tumours is done for the purpose of defining the most aggressive component of the disease and to remove all macroscopic tumour foci (**Grade B**).
- Frozen section diagnosis is of limited usefulness due to the often small foci of poor prognostic disease (invasive implants, heterogeneity of mucinous LMP tumours) (**Grade B**).
- Chemotherapy does not result in increased disease-free survival (**Grade B**).

- Surgical removal of clinically normal lymph nodes has no therapeutic benefit **(Grade B)**.
- Random peritoneal biopsies have no place in surgery for LMP tumours **(Grade B)**.
- Initial surgery for mucinous LMP tumours should include an appendectomy **(Grade B)**.
- Fertility-sparing surgery in patients with LMP tumours (including cystectomy of Stage I tumours) is an option, and probably does not affect disease-free survival **(Grade C)**.
- Recurrent disease should be primarily managed surgically **(Grade B)**.
- A “clearing hysterectomy” or “clearing oophorectomy” after completion of childbearing is not recommended **(Grade C)**.
- Specific clinical follow-up (pelvic examination, ultrasound, Ca125) is not needed in the absence of poor prognostic features **(Grade C)**.

Individual recommendations have been graded according to the level of evidence on which they are based:

Grade A: Randomized trials.

Grade B: Other robust experimental or observational studies.

Grade C: More limited evidence, but the advice relies on expert opinion and has the endorsement of respected authorities.

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