Borderline or malignant ovarian tumour?
A case report of decision making with morphometry

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SUMMARY A young woman presented with bilateral ovarian tumours. Multiple sections of each tumour were shown to many pathologists for consultation; some considered the tumours to be borderline, whereas others thought that one or both of them was malignant. Morphometry showed that the numerical classification probabilities for borderline tumour were 0·78 for the left ovarian tumour and 0·85 in the right. The lesions were therefore regarded as borderline tumours1 and no additional chemotherapy was given.

Three years after the second operation the patient is alive and well without clinical or biochemical evidence of recurrence. Most patients with borderline tumours who die from the disease do so in the first two years after the operation. This young patient was prevented from severe overtreatment by the application of morphometry, illustrating its use in this area of diagnostic gynaecopathology.

Previous studies have shown considerable disagreement among pathologists in the subjective distinction between borderline and malignant ovarian tumours.23 Although this may be of little clinical importance, there are several conditions in which discrepancies in diagnosis result in considerable differences in treatment. Application of morphometry to a predefined set of borderline and malignant tumours has, however, resulted in a classification rule with a satisfactory diagnostic quality.1 Routine application in our laboratory over a period of four years has regularly corrected the original grade of tumour assigned with qualitative subjective evaluation.4 We describe here a patient in whom morphometry was essential in the therapeutic decision making process.

Material and methods

MORPHOMETRIC ANALYSIS

The derivation of the morphometric classification rule to distinguish between borderline and malignant ovarian tumours has been described in detail elsewhere.1 Therefore, in this paper only a summary of the morphometric analysis and classification will be given.

Four micrometre thick paraffin sections stained with standard haematoxylin and eosin were used for the measurements. Multivariate analysis showed that many of the 32 morphometric features investigated were interrelated. The most important feature for the classification is the mitotic activity index (the number of mitoses at ×400 magnification in 25 fields, the diameter of each field used being 450 μm). The fields selected for counting were the most cellular ones, with the severest atypicality and highest mitotic rate. Having started in a certain area, 24 additional contiguous fields were selected randomly. Only definite mitotic figures were counted, with doubtful structures excluded.

The second best discriminator, which adds to the discriminating power of the mitotic rate, is the percentage of epithelial tissue compared with the stroma. Measurements were performed with a 42 point test grid (90 × 77 mm) according to Weibel.5 The point grid was placed on a projection microscope at ×200 magnification.

The three other features which are important are the mean nuclear area (μm²), the mean nuclear perimeter (= circumference), and the mean nuclear axis (both μm). These were assessed in 25 epithelial cell nuclei photographed at ×1000 magnification. The nuclei were randomly selected in the most cellular areas of the tumour, assessed subjectively. The morphometric technique was used selectively—that is, in the areas selected by a skilled pathologist as morphologically the most atypical. Table I shows the detailed measurements used.

The multivariate classification rule calculates a numerical probability, which ranges from 0·0 to 1·0,
that the tumour belongs to the borderline class. If the numerical classification probability was above or equal to 0.60, the tumour was regarded as borderline; if below or equal to 0.40 as malignant; and in between these values as doubtful. Such a numerical probability should not be confused with a nuclear to cytoplasmic area ratio. The numerical classification probability is calculated on the basis of the five histomorphometric and cytomorphometric features described above. It is important to remember that these five features independently contribute to the discriminating power in the multidimensional decision space.

The cases in the original study\textsuperscript{1} consisted of 10 borderline and 22 malignant cases, with the clinical outcome known. The original diagnoses were made by Professor Langley, Manchester. The criteria used for placing a tumour in the borderline category were:

1 The absence of invasion

2 The presence of two or more of the following features: multilayering of the epithelium; nuclear abnormality; "budding"; mitotic activity.

The morphometric classification rule also had prognostic importance.\textsuperscript{1} Routine application of this morphometric classification rule over a period of four years in our laboratory has corrected the original subjective rate assigned.\textsuperscript{4} So far, more than 200 ovarian tumours of the common epithelial type have been investigated, including about 40 borderline cases. Results have shown that it is also possible to predict which borderline tumours will survive or are likely to have favourable outcomes (unpublished observations).

**CASE REPORT**

A 24 year old woman presented with both ovaries enlarged, the left more than the right. The left ovary was therefore removed, without spill. There were no signs of malignancy in the peritoneal cavity, and extensive staging procedures were all negative.

The tumour measured 9 × 8 × 6 cm, and the outer surface was smooth. When cut open several cysts were seen, with many papillary structures. Multiple sections were made; the most atypical areas are shown in Figs. 1 and 2.

At clinical examination six months later, the remaining right ovary was more enlarged. Laparotomy was repeated in June 1981. There were multiple adhesions, but again no signs of malignancy. Extensive staging was negative. A tumour similar to the first one was removed, without spill.
This tumour measured $9 \times 7 \times 5$ cm with a similar pattern (a multicystic tumour with papillary protrusions). Again, multiple sections were made, and the most atypical area is shown in Fig. 3.

**Results**

The slides were shown to many pathologists, whose opinions showed considerable disagreement: some thought that the tumours were borderline, others malignant.

Table 2 summarises the clinical conditions in which the distinction between borderline and malignant ovarian tumour may be clinically important. Clearly, the present case was in the second category. Indeed, we considered whether we should treat the

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*Fig. 2  First tumour. Note the moderate nuclear atypia and pseudomultilayering due to tangential cutting. Haematoxylin and eosin. Original magnification $\times 400$."

*Fig. 3  Second tumour. The dense lymphocytic infiltrate gives the impression of high cellularity and unfavourable nuclear to cytoplasmic ratios (due to optical illusion). Haematoxylin and eosin. Original magnification $\times 100$."
Borderline or malignant ovarian tumour?

Table 2  Clinical conditions in which the distinction between borderline and malignant ovarian tumour can be important

<table>
<thead>
<tr>
<th>Condition</th>
<th>BO</th>
<th>FIGO</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FIGO IA with rupture</td>
<td>BO: no therapy</td>
<td>Grade I: chemotherapy</td>
<td></td>
</tr>
<tr>
<td>2 FIGO I with later occurring contralaterality</td>
<td>1st BO, 2nd grade I: no therapy</td>
<td>1st grade I: 2nd grade I: chemotherapy</td>
<td></td>
</tr>
<tr>
<td>3 FIGO II-IV</td>
<td>BO: no therapy</td>
<td>Grade I: debulking and chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

BO = borderline.
FIGO = clinical stage (according to the International Federation of Gynecology and Obstetrics).

It is important to distinguish between borderline and malignant ovarian tumours, because in that case the second tumour could have been regarded as a metastasis.

Application of morphometry and calculation by the computer of the numerical classification probability of both tumours showed, however, that both tumours should be regarded as borderline. The classification probability of the first tumour was 0.78, and of the second 0.85. None of the borderline tumours in the basic material had classification probabilities below 0.60, and none of the malignant tumours above 0.40. Thus both tumours of this young patient were clearly regarded as borderline.

No further treatment was given, and a conservative approach was adopted. At regular follow up no signs of malignancy were apparent, and three years after the last operation the patient is without clinical or biochemical evidence of recurrence.

Discussion

This case report illustrates the value of morphometry in diagnostic histopathology. In doubtful cases, quantitative microscopical techniques can be used for objective decision making.

We emphasise that morphometry should be applied selectively—that is, a skilled pathologist has to select the areas, cells, and nuclei of interest. In this selective diagnostic morphometry the following steps can be discerned:

1 Selection of relevant areas, cells, nuclei, etc by a skilled pathologist
2 Measurement of relevant features
3 Comparison of these quantitative features with the typical “image” in the memory in the computer
4 Classification on the basis of these results.

Clearly, the first step is important and in fact is used in everyday diagnostic pathology. This step is highly reproducible providing the pathologist is accurate and well trained. The advantage of the second step over routine qualitative subjective evaluation is that the features thus measured are quantitative and, when carefully controlled, highly reproducible. In the third step, the typical image in the memory of the computer is fixed. In contrast to the typical images in the human mind, no distracting factors can influence this reference (standard). The fourth step is equally stable for the same reasons. After three years of follow up the patient is free of clinical or biochemical evidence of recurrence. If borderline tumours do recur, it is usually within two years and this has also been our own experience. In this patient active treatment with chemotherapy was considered but was rejected in the face of the morphometric evidence.

Other examples of the clinical usefulness in individual patient care have been described in the distinction of endometrial hyperplasia from carcinoma and in follicular thyroid carcinoma.

The simplicity and usefulness of morphometric techniques make them attractive. Moreover, the methods are now relatively inexpensive and applicable to a wide range of diagnostic problems.

This work was supported in part by grant 28–343 of the Praeventiefonds.

The authors thank Mrs DIM de Jong for typing the manuscript.

References


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Borderline or malignant ovarian tumour? A case report of decision making with morphometry.

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*J Clin Pathol* 1984 37: 1110-1113
doi: 10.1136/jcp.37.10.1110

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