Advances in sub-classification of ovarian carcinomas by cell type: an update

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Abstract

The histological classification of ovarian carcinomas has changed in recent decades. The five cell types that comprise the vast majority of cases are: high grade serous, low grade serous, endometrioid, clear cell and mucinous, and the criteria for distinguishing these types have evolved. Clinical, epidemiological, pathological and molecular evidence indicates that these cell types reflect different diseases. In particular, it has become clear that high and low grade serous carcinomas are sufficiently distinctive to warrant separate classification rather than different grades of a single type of carcinoma. High grade serous carcinoma causes the vast majority of ovarian cancer deaths and is the appropriate target for screening studies.

Keywords carcinosarcoma; clear cell carcinoma; endometrioid carcinoma; fallopian tube carcinoma; histopathology; malignant Brenner tumour; mucinous carcinoma; ovarian carcinoma; serous carcinoma

Introduction

Our understanding of the aetiology and pathogenesis of ovarian cancer has undergone major shifts in the past decade. Morphological and molecular studies have supported a new dualistic model of pathogenesis.[1,2] Concomitantly, the source of high grade serous carcinoma, which causes most ovarian cancer deaths, appears more and more likely to be the fallopian tube in a majority of cases. This is supported by numerous morphological and molecular studies as well as studies in animal models.[1–7] It is essential for all types of biological studies of cancer to have a firm foundation in histopathology to bridge basic science with clinical medicine. Accordingly, accurate histological classification is essential for a complete and meaningful understanding of ovarian cancer.

There is a wide variety of types of benign and malignant ovarian tumours. There are three fundamental groups of ovarian tumours: epithelial, stromal and germ cell. Tumours of each of these groups can be benign or malignant. Malignant germ cell tumours are rare and occur mainly in children and young women. Malignant stromal tumours occur at all ages and are also uncommon. When one speaks of "ovarian cancer," this generally refers to invasive carcinoma in the epithelial group. Clinical and epidemiological studies of ovarian cancer, unless further specified, refer only to these invasive carcinomas.

There are five major subtypes of invasive ovarian carcinoma: high grade serous, low grade serous, clear cell, endometrioid and mucinous carcinoma. It has become clear over the last decade that these are not simply morphologic variants, but actually reflect different diseases. This is based on major differences in clinical, pathological and molecular features.[8]

Both pathological and clinical studies of ovarian cancer have significant limitations that directly depend on histopathology. Central pathology review, use of standardized diagnostic criteria and maximizing interobserver diagnostic reproducibility are all essential components of any study that is expected to produce reliable, biologically accurate and clinically relevant results. The most advanced molecular biological techniques are of limited value if the tissue from which the specimen was derived has not been properly classified according to current, standardized, accurate and reproducible criteria. Although the older literature suggests significant problems in diagnostic reproducibility, more recent studies have confirmed that subtyping of ovarian carcinoma is highly reproducible when standardized diagnostic criteria are used.[9,10]

Diagnostic criteria for all of the major cell types of ovarian carcinoma have undergone major shifts over the past two decades.[8–13] Several problematic areas of differential diagnosis have been addressed and clarified, and there is relative agreement on these points by expert gynaecological pathologists. Although each of these areas would seem relatively minor, when viewed cumulatively, the changes in diagnostic criteria can and do have an impact on the results of studies aimed at defining molecular and clinical features of the different subtypes.[14]

Serous carcinomas have been more clearly distinguished from endometrioid and clear cell carcinomas with which they have not infrequently been confused.[12–15] Serous carcinomas have also been divided into two distinctive groups, low grade and high grade, which do not appear to be different grades of the same tumour, but rather, based on morphologic and molecular biologic data, reflect different cell types.[8,16,17] Finally, mucinous carcinomas involving the ovaries have been refined into noninvasive, invasive and metastatic groups such that only primary invasive mucinous carcinomas are properly included under the rubric of "ovarian carcinoma".[18] Subclassification of ovarian carcinomas into the different cell types is critical because these histotypes are actually different diseases.[1,8] The concept that the cell types are different diseases is supported by cell type-specific associations with risk factors, extent of protection by tubal ligation, clinical presentation, patient age, surgical-pathologic stage, endometriosis, infertility, salpingitis, BRCA gene mutations, immunohistochemical and molecular features, response to particular treatments and survival. Accordingly, accurate assessment of cell type is critically important in ovarian cancer studies related to epidemiology, aetiology, pathogenesis, screening, prevention and treatment. Below is the summary of the dualistic model, the histological criteria for diagnosing the subtypes, and highlighting of the pitfalls and differential diagnosis of several key distinctions.

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Dualistic model

A new model of ovarian carcinogenesis divides carcinomas into two broad groups.[1] Type I tumours arise in pre-existing benign and atypical proliferative (borderline) tumours and endometriosis, usually present in low stage (FIGO stage I and II) and progress slowly. These are characteristically low grade serous, endometrioid, mucinous and most clear cell carcinomas. Type II tumours arise in fallopian tube epithelium as serous tubal intraepithelial carcinoma, present in stage III or IV, and progress rapidly. These are high grade serous carcinomas and carcinosarcomas. There are distinctive molecular correlates of the cell types which are reviewed elsewhere.[1]

High grade serous carcinoma

The most common subtype of ovarian carcinoma is high grade serous carcinoma This type and its variants (carcinosarcoma and perhaps undifferentiated carcinoma; see below) nearly always present in FIGO stages III and IV, comprise 72% of ovarian carcinomas and cause the vast majority of ovarian cancer deaths (about 85%). This latter point is critically important in the development of a screening test, as earlier detection of this subtype has at least the potential to have the greatest impact on mortality, although it remains to be demonstrated that early detection does in fact influence mortality.

The grading of serous carcinoma has been recently standardized and two points have been clarified. First, only two grades are needed; cases that appear to be of intermediate grade behave as high grade serous carcinomas and should be classified with them. Second, high grade and low grade serous carcinomas have sufficient morphologic and molecular biological and behavioural differences that they in fact reflect different cell types. The excellent prognosis associated with LGSC has been confirmed by a variety of investigators.[16,17]

Typical HGSC is characterized by papillary, glandular and solid patterns and variants of these. The solid pattern displays cohesive sheets of poorly differentiated malignant cells. Necrosis is common in both geographic and single cell patterns (Figure 1). A papillary pattern is common and may be manifested as microopapillae, small solid nests haphazardly infiltrating the stroma, or large papillae. Large thick papillae resembling transitional cell carcinoma of the urinary tract may be seen. A glandular and cribriform pattern may occur, and although this may resemble endometrioid adenocarcinoma, the glandular pattern of HGSC displays more irregularly shaped and sized glands with much higher nuclear grade, and lacks confirmatory endometrioid features (see below). One of the most characteristic and common patterns of HGSC is a solid pattern punctuated by slit-like spaces (Figure 2). Psammoma bodies are seen in over 80% of cases and are often numerous. A carcinoma with psammoma bodies in the female peritoneum is highly suggestive of serous carcinoma. This association with psammomatous calcification extends to low grade serous carcinoma, occasional clear cell carcinomas and endometrial serous carcinomas and is therefore not site or cell-type-specific.

The cytologic features of HGSC are distinctive. High grade nuclear features with scattered markedly enlarged, bizarre nuclei are common (Figure 1). Large prominent nucleoli may be present and mitotic figures are often numerous and atypical. Specimens obtained after neoadjuvant chemotherapy may display even more bizarre nuclear features.

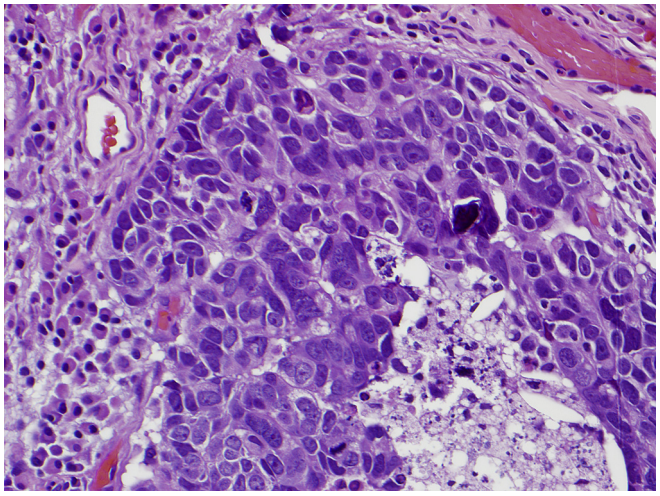

Figure 1 High grade serous carcinoma displaying a solid pattern with rare gland spaces, high nuclear grade and necrosis.

There is an evolving consensus that HGSC does not actually arise in the ovary, but rather, arises from a precursor lesion, serous tubal intraepithelial carcinoma, usually found in the tubal fimbriae and spreads from there to ovarian and peritoneal surfaces.[1–3] The traditional criteria for separating ovarian, peritoneal and tubal serous carcinomas are now recognized as quite arbitrary; extrauterine HGSC essentially refers to one disease.

Low grade serous carcinoma

LGSC is a distinctive type of ovarian cancer and comprises about 5% of ovarian carcinomas. Because these tumours arise from noninvasive precursors (serous cystadenoma and atypical proliferative serous tumour/serous borderline tumour), portions of LGSC are morphologically noninvasive. Because of this, invasion may be seen only in a minority of sections and therefore extensive sampling of apparently noninvasive tumours is important. Invasive LGSC, characteristically displays small solid nests haphazardly infiltrating the stroma (Figure 3). The noninvasive component, when present, characteristically displays a nonhierarchical pattern of papillary branching. The micropapillae may

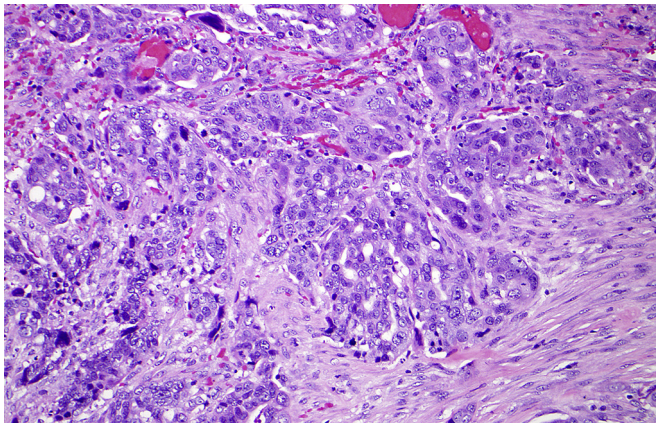

Figure 2 High grade serous carcinoma characterized by a slit-like pattern of markedly atypical epithelial cells.