Subclassification of ovarian cancer based on pathology and genetics

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Carcinomas (surface epithelial-stromal tumours) are the most common types of ovarian cancer (90%) [1,2]. Unlike colorectal carcinoma, a progression model for ovarian carcinoma has not been described. Ovarian epithelial tumours are heterogeneous and primarily classified according to cell type into serous, mucinous, endometrioid, clear, transitional, and squamous cell tumours [1,2]. According to the WHO classification, tumours in each of these categories are further subdivided into benign, borderline (intermediate), and carcinoma forms, which are associated with different prognoses. This is done according to the amount of epithelial cell proliferation, the degree of nuclear atypia, and the presence or absence of stromal invasion [1,2]. In spite of significant improvements in cytoreduction and chemotherapy, the overall outcome of patients with ovarian cancer continues to be poor.

Currently, however, based on light microscopy and molecular genetics, ovarian carcinoma is subdivided into five main subtypes which, in descending order of frequency, are: high-grade serous carcinomas (HGSC), clear cell carcinomas (CC), endometrioid carcinomas (EC), mucinous carcinomas (MC), and low-grade serous carcinomas (LGSC). These five subtypes account for 98% of ovarian carcinomas, can be reproducibly diagnosed, and are inherently different diseases, as indicated by differences in epidemiological and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, response to chemotherapy, and outcome. These differences are the subject of this presentation. With progress towards subtype specific management of ovarian carcinoma, accurate subtype assignment by surgical pathologists is becoming increasingly important.

Serous tumours

HGSC are the most common ovarian carcinomas (70%) and most patients present with high stage disease; tumour confined to the ovary at diagnosis is distinctly uncommon [3]. Recent studies indicate that serous borderline tumours (SBTs) and conventional serous carcinomas represent separate pathogenetic entities. SBTs frequently display *B-Raf/K-ras* mutations but rarely mutant *p53* [4]. In contrast, *B-Raf/K-ras* mutations are very rare in HGSC, but *p53* and *BRCA* mutations occur in approximately 60% of cases [3].

A dualistic model for ovarian serous carcinogenesis has been recently proposed [4]. One pathway would involve a stepwise progression from SBT to noninvasive SBT with micropapillary pattern, and then invasive LGSC. The other pathway would allow rapid transformation of the ovarian surface epithelium into a HGSC. Gene expression profiling has recently revealed that HGSCs show enhanced expression of genes linked to cell cycle control (S and G_2-M checkpoint regulation), chromosomal instability (*STK6*, *E2F3*), and *BRCA* epigenetic silencing [5]. These alterations are absent in SBTs and LGSC.

Mucinous tumours

Mucinous ovarian tumours are often heterogeneous, benign-appearing, borderline, and noninvasive and invasive patterns may coexist within an individual neoplasm. Such morphologic continuum suggests that tumour progression occurs from cystadenoma and borderline tumour to noninvasive, microinvasive, and invasive carcinoma. This hypothesis is supported by studies of *K-ras* mutations which are common in mucinous ovarian tumours and represent an early event in mucinous tumourigenesis. Mucinous borderline tumours have a higher frequency of *K-ras* mutations than that of mucinous cystadenomas but a lower rate than that of mucinous carcinomas [6].

Almost all ovarian mucinous borderline tumours associated with pseudomyxoma peritonei are secondary to low-grade mucinous tumours of the appendix [1, 2].

Primary ovarian MCs are very rare, accounting for only 3% of mucinous ovarian tumours. The most important differential diagnosis is with metastatic MC that may present clinically as a primary ovarian tumour. Most of these originate in the large intestine, appendix, pancreas, biliary tract, stomach, or cervix.

Most primary MCs of the ovary are unilateral and stage I.

Endometrioid tumours

Endometrioid ovarian tumours resemble those encountered more frequently in the endometrium and recent molecular genetic studies suggest that, in most cases, they arise due to the malignant transformation of endometriosis and not the ovarian surface epithelium [7]. Endometrioid borderline tumours usually have beta-catenin gene (*CTNNB1)* mutations.

ECs account for 10% of all ovarian carcinomas and most of them are diagnosed at stage I or II [1]. The most common genetic abnormalities identified in sporadic EC of the ovary are somatic mutations of the beta-catenin (*CTNNB1*) and *PTEN* genes and microsatellite instability [8]. Compared with uterine EC, the ovarian tumours have a similar frequency of β-catenin abnormalities but a lower rate of microsatellite instability (MI) and *PTEN* alterations [8].

Simultaneous carcinomas of the uterine corpus and ovary, usually detected as synchronous and less frequently as metachronous tumours, occur in 15 to 20% of ovarian tumours and in approximately 5% of uterine tumours [9]. Both tumours are of endometrioid type in the majority of cases. Accurate diagnosis as separate independent primary tumours, or as primary tumour in one site with metastasis to the other site, has important prognostic implications. Clonality analysis using various molecular methods can also be helpful. These include loss of heterozygosity, gene mutation, and clonal X-inactivation analysis [10].

Clear cell carcinomas

This is the most enigmatic subtype of ovarian carcinoma. CCs account for approximately 10% of ovarian carcinomas and patients typically present with stage 1 or 2 disease. CCs are associated with a relatively unfavourable prognosis, compared to other low stage ovarian carcinomas. As with EC, there is an association with endometriosis, and CCs associated with endometriosis have a favourable prognosis.

Very little is known about the genetic alterations of CCs. They lack the *BRCA* abnormalities, chromosomal instability, or complex karyotypes of HGSC [11]. CCs are usually positive for HNF1-β and are negative for ER and WT1 in more than 95% of cases [12].

CCs are less likely to respond to chemotherapy than HGSCs. Whereas highly proliferative cells that lack the ability to repair double stranded DNA (i.e. HGSC cells) can be anticipated to show sensitivity to platinum-based chemotherapy, the less proliferative, genomically stable cells of CC can similarly be anticipated to be less sensitive to platinum compounds. At this point there are no clearly superior alternatives to platinum-based chemotherapy.

Conflict of interest statement

None declared.

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