Abstract Malignant epithelial tumours (carcinomas) are the most common ovarian cancers and the most lethal gynaecological malignancies. Based on light microscopy and molecular genetics, ovarian carcinomas are subdivided into at least five main subtypes that account for over 95% of cases 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. For successful subtype-specific treatment, reproducible pathological diagnosis of tumour cell type is critical. Recent investigations have also demonstrated that a significant number of cancers traditionally thought to be primary ovarian tumours (particularly serous, endometrioid and clear cell carcinomas) originate in the fallopian tube and the endometrium and involve the ovary secondarily. In this review we summarise recent advances in the molecular pathology, which have greatly improved our understanding of the biology of ovarian carcinoma and are also relevant to patient management.

Keywords Ovary · Carcinoma · Pathology · Molecular genetics

Ovarian epithelial tumours are heterogeneous and primarily classified according to cell type into serous, mucinous, endometrioid, clear cell, transitional and squamous cell tumours [1]. According to the World Health Organization (WHO) classification [2], neoplasms in each of these categories are further subdivided into benign, borderline (intermediate) and malignant (carcinoma) forms, which are associated with different prognoses. This is done microscopically according to the amount of epithelial cell proliferation, the degree of nuclear atypia (mild, moderate and severe) and the presence or absence of stromal invasion [1, 2]. Borderline tumours (also designated as tumours of low malignant potential) show epithelial proliferation greater than that seen in their benign counterparts, variable nuclear atypia, but an absence of stromal invasion, and are associated with much better prognosis than carcinomas. Despite this lack of invasiveness within the ovary, serous borderline tumours can either implant on peritoneal surfaces or be associated with independent foci of primary serous peritoneal neoplasia and, rarely (about 10% of peritoneal implants), invasion of the underlying tissues occurs. The biologic behaviour of invasive peritoneal implants is similar to that of well differentiated (low-grade) serous carcinomas.

Malignant epithelial tumours (carcinomas) are the most common ovarian cancers, accounting for 90% of cases, and are the most lethal gynaecological malignancies [1]. In spite of significant improvements in cytoreduction and chemotherapy, the overall outcome of patients continues to be poor. Unlike colorectal carcinoma, a progression model for ovarian carcinoma has not been described. Currently, however, based on light microscopy and molecular genetics, ovarian carcinoma is subdivided into at least five main subtypes which, in descending order of frequency, are high-grade serous carcinomas (HGSC), clear cell carcinomas (CCC), endometrioid carcinomas (EC), mucinous car-
cinomas (MC) and low-grade serous carcinomas (LGSC) (Fig. 1, Table 1) [3]. These tumours 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 review. With progress towards subtype-specific management of ovarian carcinoma, reproducible pathological diagnosis of tumour cell type is critical.

Serous carcinomas

Recently, it has been recognised that LGSC and HGSC are fundamentally different tumour types [4, 5]. The former are associated with a serous borderline component in most cases and are not related to BRCA abnormalities. In contrast, HGSCs are not associated with serous borderline tumours and may arise from the fallopian tube in a significant number of cases [6, 7]. Because of the fundamental differences between HGSC and LGSC, they are considered distinct subtypes and will be discussed separately.

High-grade serous carcinomas (HGSC)

These are the most common ovarian carcinomas and most patients present with high-stage disease; tumour confined to the ovary at diagnosis is distinctly uncommon [8]. The most distinctive growth pattern consists of highly stratified epithelium with slit-like spaces. The tumour cells are typically of intermediate size, with scattered bizarre mononuclear giant cells; prominent nucleoli are common. The mitotic rate is very high (Fig. 1a). In contrast to LGSCs, these tumours show more than 3-fold variation in nuclear size.

Most HGSCs have abnormalities of BRCA1 or BRCA2 (germline or somatic mutation or, in the case of BRCA1, promoter methylation and loss of expression) and TP53...