

## REVIEW

# Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis

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### Summary

Ovarian carcinomas comprise a heterogeneous group of neoplasms, the four most common subtypes being serous, endometrioid, clear cell and mucinous. In recent years, our understanding of the underlying pathogenesis and initiating molecular events in the different tumour subtypes has greatly increased, and although ovarian carcinoma is often considered clinically as one disease, there is now a much greater realisation that the various subtypes have a different natural behaviour and prognosis. At present, adjuvant therapy is mainly dependent upon tumour stage and grade rather than type; however, this is likely to change in the future with the development of new chemotherapeutic agents and targeted therapies and clinical trials are necessary to evaluate the efficacy of different agents in clear cell, mucinous and low grade serous carcinomas, neoplasms which are considered relatively resistant to traditional chemotherapeutic regimes. In this review, the major subtypes of ovarian carcinoma are discussed. It is now firmly established that there are two distinct types of ovarian serous carcinoma, low grade and high grade, the former being much less common and arising in many cases from a serous borderline tumour. Low grade and high grade serous carcinoma represent two distinct tumour types with a different underlying pathogenesis rather than low grade and high grade variants of the same neoplasm. Both are usually advanced stage (stage III or IV) at diagnosis. B-raf and k-ras mutations are important molecular events in low grade serous carcinomas while high grade serous carcinomas are almost always associated with TP53 mutation. There is now emerging and compelling evidence that many high grade serous carcinomas (by far the most common subtype of ovarian carcinoma) actually arise from the epithelium of the distal fallopian tube. Future studies regarding the initiating molecular events in the development of this aggressive neoplasm should concentrate on this site. Primary ovarian mucinous carcinomas are uncommon, almost always unilateral and stage I, and largely of so-called intestinal or enteric type. Most arise in a stepwise manner from a pre-existing mucinous cystadenoma and mucinous borderline tumour. Endometrioid and clear cell carcinomas typically present as low stage neoplasms and in many, or most, cases arise from endometriosis; the former are usually well differentiated and there is now evidence that the majority of neoplasms reported in the past as high grade endometrioid carcinoma are of serous type. WT1 is useful in this regard since it is a relatively specific marker of a serous phenotype. It is recommended that different subtypes of ovarian carcinoma are graded

using different systems rather than employing a universal grading system.

*Key words:* Ovary, carcinoma, pathogenesis, typing.

Received 14 March, revised 27 April, accepted 28 April 2011

### INTRODUCTION

In most developed countries, ovarian carcinoma is the second most common malignancy of the female genital tract, following endometrial carcinoma. The majority of cases are diagnosed at advanced stage (III or IV) and the overall prognosis is poor. Although clinically often considered as one disease, there is an increasing realisation that the different morphological subtypes of ovarian carcinoma have a different pathogenesis, are associated with distinct molecular alterations, and have a different natural history and prognosis.<sup>1–4</sup> Many clinical studies lump the different morphological subtypes together, with the result that it is difficult to tease out the behaviour of the various tumour subtypes; with our current state of knowledge, this is no longer appropriate. Given these factors and the realisation that some tumour subtypes, for example clear cell, mucinous and low grade serous, do not respond well to traditional ovarian chemotherapeutic agents, and that ongoing trials are investigating the efficacy of different agents in some of these tumour subtypes, it is clear that accurate pathological typing of ovarian carcinomas is becoming more important and may be critical in the future in directing therapy. To this end, it is recommended that central pathology review becomes mandatory in ovarian carcinoma trials when treatment is dependent upon the morphological subtype or any other pathological parameter. Typing may also be of importance in directing investigations to rule out an inherited genetic condition; for example, a young woman with a high grade serous carcinoma could have an underlying BRCA1 or BRCA2 germline mutation while a clear cell carcinoma may be a manifestation of underlying Lynch syndrome (hereditary non-polyposis colorectal cancer syndrome). It is also possible that typing may become important in clinically stage I ovarian carcinomas in determining the need for lymphadenectomy, since it has been shown that serous carcinomas are more likely than other morphological types to be associated with lymph node metastasis in clinically presumed stage I disease.<sup>5</sup>

In this review, the major morphological subtypes of ovarian carcinoma and problematic areas in typing are discussed. Although typing of most cases is straightforward on morphology alone, immunohistochemistry may assist in problematic cases. Before discussing the major subtypes of ovarian carcinoma, some general issues regarding the relative frequencies of the

**Table 1** Relative frequencies of subtypes of ovarian carcinoma based on two recent population based studies

68–71% serous
3% mucinous
9–11% endometrioid
12–13% clear cell
1% transitional
6% mixed

various tumour types, morphological changes secondary to chemotherapy and tumour grading are covered.

### RELATIVE FREQUENCIES OF MAJOR MORPHOLOGICAL SUBTYPES OF OVARIAN CARCINOMA

The major morphological subtypes of ovarian carcinoma are serous, endometrioid, clear cell and mucinous.<sup>6</sup> Other subtypes include transitional, undifferentiated and mixed. Primary ovarian squamous carcinomas also occur; these are rare, usually arise in a dermoid cyst or more uncommonly in association with endometriosis or a Brenner tumour, and will not be discussed further. Two relatively recent population based studies which have included central pathology review using modern diagnostic criteria have provided updated information regarding the relative frequencies of the major subtypes of ovarian carcinoma<sup>7,8</sup> (Table 1). It can be seen that serous is the most common, followed by clear cell and endometrioid which occur with approximately equal frequency. Mucinous carcinomas are less common. This represents a change from most older studies where mucinous carcinoma was the second most common subtype and accounted for approximately 12% of primary ovarian carcinomas,<sup>9</sup> a much higher frequency than in the two recent studies; reasons for this decline in the frequency of mucinous carcinoma are discussed later. The two studies also indicate an increase and decrease in the frequency of serous and endometrioid carcinoma, respectively; this is likely a reflection of the fact that the distinction between a high grade serous and high grade endometrioid carcinoma was previously poorly reproducible<sup>10–14</sup> and there is now a realisation that many neoplasms which were previously diagnosed as advanced stage, high grade endometrioid carcinoma were, in fact, of serous type (discussed later). When divided into early stage (stage I–II) and late stage (stage III–IV), it can be seen that serous, clear cell and endometrioid carcinomas are approximately equally represented in early stage, nearly all mucinous carcinomas are early stage and a very high percentage of advanced stage neoplasms are serous in type (Table 2). Put another way, a high percentage of clear cell, endometrioid and mucinous carcinomas are diagnosed at early stage and in fact these tumour types (especially endometrioid and mucinous) are usually confined to the ovary at diagnosis (stage I).

**Table 2** Early stage (I/II) versus late stage (III/IV) distribution of subtypes of ovarian carcinoma based on two recent population based studies

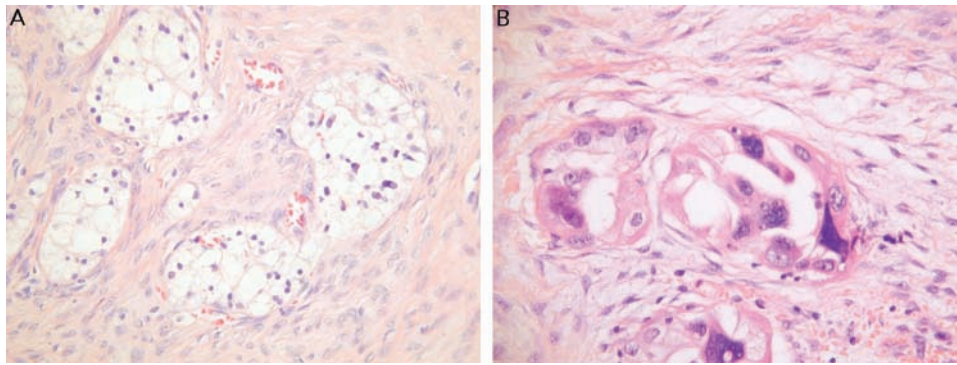
	Stage I/II	Stage III/IV
Serous	36%	88%
Clear cell	26%	5%
Endometrioid	27%	3%
Mucinous	8%	1%

### MORPHOLOGICAL CHANGES IN OVARIAN CARCINOMAS SECONDARY TO CHEMOTHERAPY

For many years, the traditional management of advanced stage ovarian carcinoma has been surgical debulking followed by adjuvant chemotherapy. However, in an increasing number of cases, upfront chemotherapy is administered, especially in patients who are a poor operative risk or patients with miliary disease or widespread metastasis where optimal debulking is not considered feasible; chemotherapy may or may not be followed by surgery. The morphological features of ovarian carcinomas treated by chemotherapy often differ markedly from native tumour.<sup>15,16</sup> Post-chemotherapy, many ovarian carcinomas (the vast majority will represent serous carcinomas since almost all advanced stage ovarian malignancies are of this morphological subtype) have abundant clear or eosinophilic cytoplasm and the nuclear features are often bizarre with multinucleate tumour giant cells<sup>15,16</sup> (Fig. 1). There may be no residual tumour or it may be difficult to identify residual neoplastic cells due to pronounced chemotherapy effect with marked fibrosis, necrosis, inflammation, cholesterol cleft formation, haemosiderin deposition and dystrophic calcification. Unless there is no or minimal response, it can be very difficult to type an ovarian carcinoma following chemotherapy and there is a tendency to misdiagnose some as clear cell carcinoma due to the abundant clear cytoplasm.<sup>15,16</sup> If upfront chemotherapy is being administered, a pre-chemotherapy tissue biopsy (usually a percutaneous radiologically guided biopsy or a biopsy taken at laparoscopy) should be obtained for definitive typing, apart from in exceptional circumstances, rather than relying on cytology of the ascitic fluid in combination with serum CA125 levels and imaging. The procurement of a tissue biopsy, as well as facilitating tumour typing and excluding a metastasis from other sites, means that material is available for future studies and research; for example, targeted therapies may be developed against specific proteins and if tissue is available this will be useful in assessing whether the target protein is present in the tumour cells. Tissue obtained at different stages in treatment may also be useful in assessing tumour progression and response to therapy.

### GRADING OF OVARIAN CARCINOMAS

Several grading systems are used for ovarian carcinoma but grading is often poorly performed by pathologists and in many studies the grading system used has not been specified.<sup>17–19</sup> Most of the grading systems are universal in that they can be applied to all the major morphological subtypes of ovarian carcinoma;<sup>17–19</sup> for example, the Shimizu-Silverberg system is based on the Nottingham grading system for breast carcinoma and uses three parameters, namely the degree of nuclear atypia, the mitotic count and the architectural features, specifically the amount of glandular, papillary or solid growth.<sup>17</sup> Each parameter is given a score of 1–3 and a grade is derived based on the summation of the scores. However, although many pathologists use this or other universal grading systems, such as FIGO or World Health Organization (WHO), there is an increasing tendency to employ different grading systems for different morphological subtypes of ovarian carcinoma; this practice has been recommended in the Royal College of Pathologists Ovarian Cancer Datasets in the United Kingdom.<sup>20</sup> Grading of the different subtypes of ovarian carcinoma is discussed with each specific tumour type.



**Fig. 1** (A) Ovarian serous carcinoma with clear cytoplasm and (B) bizarre nuclear features. These are examples of serous carcinomas with morphological features secondary to chemotherapy.

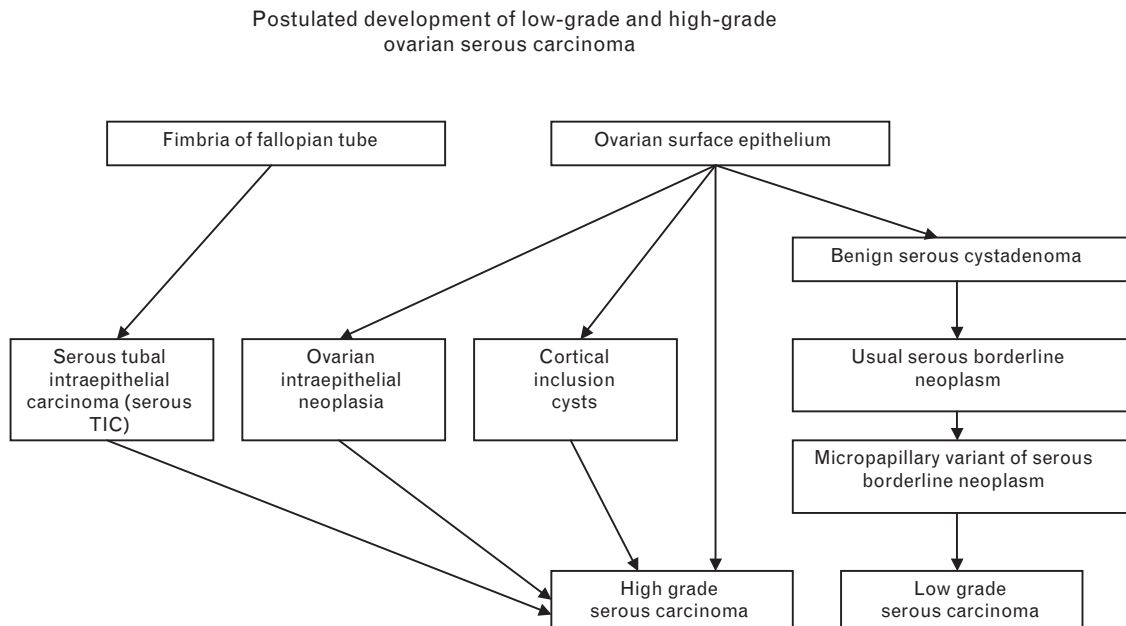
## SEROUS CARCINOMA

The perceived relationship between benign, borderline and malignant ovarian serous neoplasms was controversial and a source of confusion for many years. It has always been tempting to speculate that a continuum of ovarian serous neoplasia exists from benign to borderline to malignant. However, pathological evidence for this is lacking and until recently it was generally assumed that there was no firm relationship between borderline and malignant serous neoplasms, although occasionally the two were found to coexist. Recent studies have shed significant light on this issue and have convincingly demonstrated that there are two distinct types of ovarian serous carcinoma, low grade and high grade.<sup>1-4,21-27</sup> Although termed low grade and high grade serous carcinoma, it is important to emphasise that these are not two grades of the same neoplasm but rather two distinct tumour types with different underlying pathogenesis, molecular events, behaviour and prognosis. High grade serous carcinoma is much more common than low grade. Low grade serous carcinoma is thought to arise in many cases in a stepwise fashion from a benign serous cystadenoma through a serous borderline tumour to an invasive low grade serous carcinoma. Thus, there is a well defined adenoma-carcinoma sequence. It has been suggested that a micropapillary architecture in a serous borderline tumour is an intermediate step between a usual serous borderline tumour and an invasive low grade serous carcinoma.<sup>1,27-29</sup> However, a micropapillary architecture is not present in many serous borderline tumours with coexistent low grade serous carcinoma. I also make the point that it is relatively uncommon to see areas of invasive low grade serous carcinoma within a serous borderline tumour and conversely in many low grade serous carcinomas a borderline component is not seen. Therefore, it is not proven that all low grade serous carcinomas arise from a pre-existing serous borderline tumour and it is possible that some or many do not. In contrast, high grade serous carcinoma is not related to serous borderline tumour and was thought until recently to arise directly from the ovarian surface epithelium or the epithelium of cortical inclusion cysts with no well defined precursor lesion. There is now emerging and quite compelling evidence (discussed later) that many high grade ovarian serous carcinomas actually originate from the epithelium of the distal fimbrial portion of the fallopian tube.<sup>30-35</sup> Instead of grading ovarian serous carcinoma using a three-tiered system (well, moderate, poor; grade 1, 2 or 3), there is now a growing tendency amongst pathologists and oncologists to classify these as high grade or low grade and this practice has been adopted in the United

Kingdom;<sup>20</sup> anecdotally many gynaecological pathologists now use this two tiered grading system which was originally proposed by the MD Anderson Group (Houston, Texas, USA). The classification of a serous carcinoma as low grade or high grade has been shown to be reproducible amongst pathologists.<sup>36,37</sup> Almost all serous carcinomas which would have previously been classified as moderately or poorly differentiated represent high grade neoplasms while those which would have been classified as well differentiated may be either low grade or high grade using the two tier classification. For example, some architecturally well differentiated serous carcinomas have high nuclear grade and represent examples of high grade serous carcinoma. Although representing two distinct tumour types, on rare occasions a low grade serous carcinoma component may coexist with and probably transform into a high grade serous carcinoma or even an undifferentiated carcinoma or a high grade serous carcinoma may arise directly from a serous borderline tumour (Dehari *et al.*<sup>38</sup> and personal observations). However, most low grade serous carcinomas when they recur do so as low grade neoplasms. Some advocate the term invasive micropapillary serous carcinoma as an alternative to low grade serous carcinoma but this terminology is not recommended since some low grade serous carcinomas do not exhibit a micropapillary architecture and conversely many high grade serous carcinomas do so. Figure 2 illustrates the postulated pathways of development of low grade and high grade serous carcinoma.

### Morphological and immunohistochemical features of low grade and high grade serous carcinoma

The distinction between low and high grade serous carcinoma is based on morphology, the chief discriminator being the degree of nuclear atypia in the worst area of the tumour. The amount of mitotic activity is also taken into account.<sup>36,37</sup> In low grade serous carcinoma, the nuclei are uniform with mild or at the most moderate atypia and less than or equal to 12 mitoses per 10 high power fields (the mitotic count is usually approximately 2 per 10 high power fields or less than this) (Fig. 3). There is no necrosis or multinucleation. High grade serous carcinoma exhibits moderate to marked nuclear atypia and greater than 12 mitoses per 10 high power fields (Fig. 4). Necrosis and multinucleate cells are often present. It is generally not necessary to count mitotic figures since these are typically abundant in high grade serous carcinomas and difficult to find in low grade neoplasms. In both low grade and high grade serous carcinomas, there may be a variety of architectural patterns,



**Fig. 2** Postulated developmental pathways of low grade and high grade serous carcinoma.

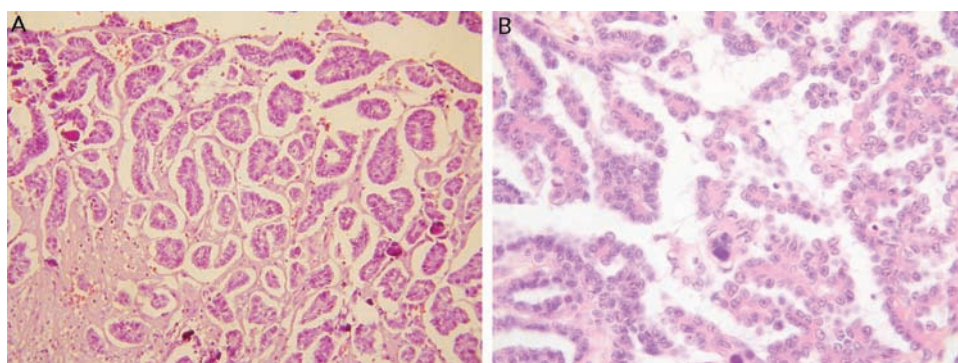
including nested, papillary (micropapillary or macropapillary), glandular (slit-like or round spaces), cribriform, solid and single cells. The glands and papillae in low grade serous carcinomas are often surrounded by clefts or non-epithelial lined spaces and intracytoplasmic mucin is often a feature.<sup>39</sup> Psammoma bodies are common in both tumour types. Psammocarcinoma is a term used for a tumour with extensive psammoma body formation and is usually morphologically a low grade serous carcinoma, although occasional examples have high grade nuclear cytology, in keeping with high grade serous carcinoma.

Both low grade and high grade serous carcinomas typically express WT1. High grade serous carcinoma exhibits significantly greater expression of p53, MIB1, bcl-2, c-kit, Her-2 neu, HLA-G and p16 than low grade serous carcinoma.<sup>40,41</sup> p16 is typically diffusely positive in high grade serous carcinoma and focally positive or negative in low grade. Low grade serous carcinomas are almost always diffusely positive with oestrogen receptor (ER), as are a high percentage of high grade serous carcinomas (70–80%). High grade serous carcinomas most commonly exhibit diffuse intense nuclear immunoreactivity with p53 but totally absent staining ('all or nothing') is also an aberrant pattern of p53 staining and suggestive of an underlying TP53 abnormality (see next section). So-called 'wild-type' p53

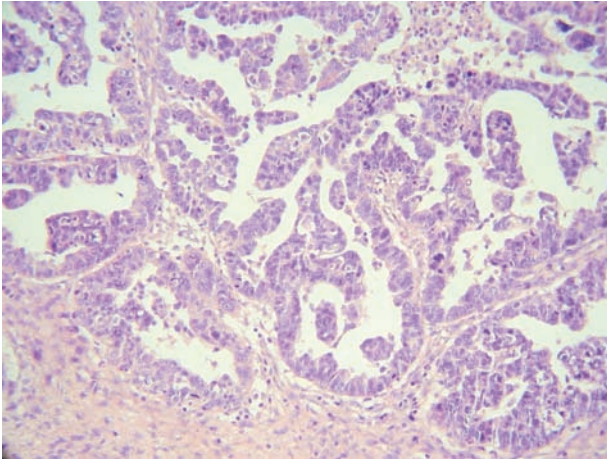
staining, with a focal, weak and heterogenous pattern, is not indicative of a TP53 abnormality and is characteristic of low grade serous carcinoma.<sup>42</sup>

#### Molecular events in low grade and high grade serous carcinoma

The underlying molecular events differ between low grade and high grade serous carcinoma. Low grade serous carcinoma is associated with k-ras or b-raf mutation in approximately two-thirds of cases.<sup>21–27</sup> These mutations occur early in the evolution of low grade serous carcinoma since they are also found in borderline and benign areas within the same neoplasm. K-ras and b-raf mutations appear mutually exclusive; in other words one, but not both, may be present in a particular neoplasm. The ERBB2 gene is also frequently mutated.<sup>27</sup> Low grade serous carcinoma is not associated with TP53 mutations.<sup>21–27</sup> In contrast, high grade serous carcinomas harbour, in most cases, a TP53 mutation or exhibit p53 dysfunction and this appears to occur early in neoplastic development,<sup>20–26</sup> they are not, except in occasional cases, associated with k-ras, b-raf or ERBB2 mutation. A recent study using stringent techniques identified TP53 mutations in 97% of ovarian high grade serous carcinomas; most of the mutation negative cases exhibited TP53



**Fig. 3** (A) Low grade serous carcinoma with a micropapillary architecture and clefts surrounding the groups of tumour cells. (B) On high power of another low grade serous carcinoma, the tumour cells are bland with little mitotic activity.



**Fig. 4** High grade serous carcinoma with slit-like spaces and abundant mitotic activity.

dysfunction, illustrating that p53 is abnormal in almost 100% of high grade serous carcinomas.<sup>43</sup> High grade serous carcinomas are also associated with BRCA1 and BRCA2 abnormalities, including germline mutations and somatic abnormalities.

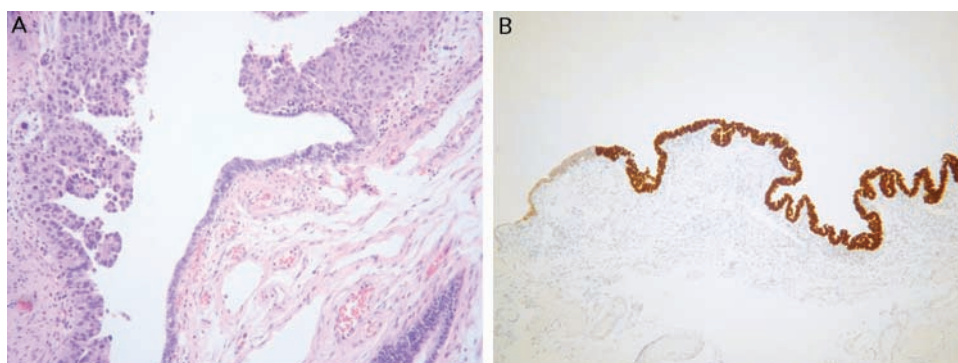
#### Behaviour of low grade and high grade serous carcinoma

Most low grade and high grade serous carcinomas are stage III or IV when diagnosed. At present, management is similar between these two tumour types and consists, in most cases, of total surgical debulking if possible followed by adjuvant chemotherapy. In cases where surgical debulking is not considered feasible, upfront chemotherapy may be the method of treatment and this may or may not be followed by surgical debulking. However, adjuvant chemotherapy is usually not administered for a stage I low grade serous carcinoma. Additionally, there is a growing realisation amongst oncologists that low grade serous carcinomas do not respond well to traditional chemotherapeutic agents and if the tumour is optimally debulked with no gross residual disease, some oncologists do not administer adjuvant chemotherapy. High grade serous carcinoma is an aggressive neoplasm which usually responds well initially to chemotherapy but which commonly recurs. Few studies have directly compared the outcome between low grade and high grade serous carcinoma. In one study, the survival of patients with low grade neoplasms was significantly better than that of patients with high grade tumours.<sup>36</sup> In this study, the 5 year survival for high grade

serous carcinoma was 9% with a median survival of 1.7 years<sup>36</sup> while low grade serous carcinomas had a median survival of 4.2 years and a 5 year survival of 40%.<sup>36</sup> In another study of low grade serous carcinomas, the median overall survival with stage III or IV disease was 6.8 years.<sup>44</sup> Low grade serous carcinomas often prove fatal but in some cases the course is indolent and in a few cases the patient survives for a considerable period of time, for example in excess of 10 or 20 years.

#### EVIDENCE FOR ORIGIN OF HIGH GRADE PELVIC SEROUS CARCINOMA FROM DISTAL FALLOPIAN TUBE

There is recent convincing and accumulating evidence that many currently classified high grade serous carcinomas of the ovary, fallopian tube and peritoneum (collectively referred to as high grade pelvic serous carcinoma) are derived from the fimbria of the fallopian tube.<sup>30–35</sup> Most of the work has emanated from Christopher Crum and colleagues in the Brigham and Women's Hospital, Boston, USA. The initial evidence for this came from prophylactic salpingo-oophorectomy specimens in patients with germline BRCA1 or BRCA2 mutation, these patients having a high risk of developing ovarian high grade serous carcinoma. In initial studies, small high grade serous carcinomas were occasionally identified in the ovary but this was rare. However, when pathologists began examining the fallopian tubes in their entirety, it was found that there was more likely to be a small *in situ* or invasive high grade serous carcinoma involving the mucosa of the fimbria of the fallopian tube; the *in situ* lesions are referred to as serous tubal intraepithelial carcinoma (serous TIC). This is relatively uncommon but is occasionally seen in prophylactic salpingo-oophorectomy specimens in patients with BRCA1 or BRCA2 germline mutation. Further studies systematically examined the fallopian tubes in patients with sporadic high grade ovarian serous carcinoma and found similar lesions involving the fimbria in a significant percentage of cases (Fig. 5).<sup>30,33</sup> Furthermore, identical TP53 mutations were demonstrated within the ovarian and tubal lesions. While this does not unequivocally prove that the origin is within the fallopian tube (this could represent a tumour originating within the ovary and spreading to the fallopian tube), there is accumulating evidence that many high grade pelvic serous carcinomas arise from the tubal fimbria from serous TIC. A p53 signature has also been demonstrated in the fallopian tube.<sup>45</sup> This takes the form of small foci of intense p53 nuclear staining involving consecutive secretory cells, most commonly of the fimbria, in the absence of morphological



**Fig. 5** (A) Serous tubal intraepithelial carcinoma (serous TIC) involving fimbria of fallopian tube and exhibiting diffuse nuclear p53 positivity; (B) the adjacent tubal epithelium is p53 negative.

changes. TP53 mutations have been demonstrated in some p53 signatures and these may represent the earliest stage of development of high grade pelvic serous carcinoma. However, p53 signatures are extremely common in the fallopian tube, even in patients with benign disease and no hereditary predisposition to developing ovarian cancer, and it is clear that only a small proportion will ever develop into a serous TIC. Serous TIC is not diagnosed on the basis of p53 staining unless associated morphological alterations are present associated with a high MIB1 proliferation index.

It is probable that not all high grade pelvic serous carcinomas are derived from the fallopian tube. A recent study which systematically examined all of the fallopian tubes in a consecutive series of ovarian carcinomas identified serous TIC in nearly 60% of high grade serous carcinomas but not in other morphological subtypes of ovarian carcinoma.<sup>33</sup> It is possible that some high grade serous carcinomas do arise from the ovarian surface epithelium or the epithelium of cortical inclusion cysts, the latter being lined by ciliated epithelium identical to that lining the fallopian tube. Another possibility in those cases in which no premalignant or malignant lesion is found in the fallopian tube is that tubal epithelium may exfoliate and become incorporated into the ovary and subsequently give rise to a high grade serous carcinoma.<sup>33</sup>

It can be summarised that there is accumulating evidence that many, or even most, high grade pelvic serous carcinomas (high grade serous carcinomas which are currently classified as ovarian, tubal or peritoneal in origin) arise from the fimbria of the fallopian tube. In most cases, the malignant cells exfoliate from the fimbria into the pelvis and abdomen and result in the formation of an ovarian mass or masses usually, but not always, with disease elsewhere in the pelvis and abdomen; this is conventionally referred to as ovarian high grade serous carcinoma. In other cases, the neoplasm remains localised to the fallopian tube, resulting in a fallopian tube high grade serous carcinoma, or gives rise to extensive peritoneal disease in the absence of significant ovarian or tubal involvement; this is conventionally referred to as primary peritoneal high grade serous carcinoma. It is likely that neoplasms which are currently classified as high grade serous carcinomas of the ovary, fallopian tube and peritoneum are all different manifestations of the same disease and the designation high grade pelvic serous carcinoma may be more appropriate. A consequence of these observations is that screening programmes for ovarian carcinoma may be relatively ineffective in downstaging high grade serous carcinomas since these are most likely disseminated from the outset. However, screening may be of value in picking up serous carcinomas when the burden of disease is lower and will also identify other morphological subtypes of carcinoma which probably do arise within the ovary. Future studies investigating the underlying molecular events in the development of high grade pelvic serous carcinoma should concentrate on the distal fallopian tube.

## MUCINOUS CARCINOMA

Primary ovarian mucinous carcinomas affect a wide age range, including occasionally children and adolescents. As discussed, they are relatively uncommon, the two studies referred to earlier suggesting that these account for approximately 3% of primary ovarian carcinomas,<sup>7,8</sup> a significantly lower percentage than in older studies. The reasons behind the apparent marked decline in primary ovarian mucinous carcinomas are

well known. In older studies, it is likely that many presumed primary ovarian mucinous carcinomas, especially of advanced stage, were metastases from extraovarian sites. Advances in imaging, serum markers and preoperative workup have resulted in better recognition of metastatic ovarian neoplasms with the result that many of these are not surgically removed. Moreover, pathologists are now better at recognising the morphological features of metastatic mucinous carcinoma in the ovary,<sup>1,46–52</sup> including the tendency to cystic change and the well known maturation phenomenon resulting in areas resembling benign and borderline mucinous cystadenoma. The use of differential cytokeratin staining and other immunohistochemical markers<sup>53–60</sup> has also improved the situation, although problems still exist. It is now clear that ovarian mucinous neoplasms associated with pseudomyxoma peritonei are almost always of appendiceal origin,<sup>61–63</sup> with the very rare exception of primary ovarian mucinous neoplasms of overtly large intestinal type arising in a dermoid cyst.<sup>64</sup> It seems to be overtly large intestinal type mucinous epithelium which has the potential to result in pseudomyxoma peritonei. There has also been a redefinition of the criteria for diagnosis of a well differentiated mucinous carcinoma with so-called expansile (non-destructive, confluent glandular) invasion;<sup>1,46–52,65,66</sup> the distinction of this from a mucinous borderline tumour at the upper end of the spectrum still represents a somewhat poorly reproducible area amongst pathologists, resulting in some variation in the reported prevalence of primary ovarian mucinous carcinoma between centres.

Most primary ovarian mucinous carcinomas are unilateral and stage I and advanced stage neoplasms (stage III or IV) are extremely uncommon. In this scenario, a secondary should always be strongly considered. Although metastatic mucinous carcinomas in the ovary are still sometimes misdiagnosed as a primary ovarian mucinous carcinoma or even a mucinous borderline tumour due to the pronounced maturation effect seen with some secondary mucinous carcinomas in the ovary, we have to some extent come full circle in that, in my opinion, there is now a tendency to overplay the possibility of a metastasis even when the pathological features are obviously those of a primary ovarian neoplasm. I feel that in a large majority of cases the distinction between a primary and secondary mucinous carcinoma in the ovary can be achieved by careful pathological examination encompassing both the gross and microscopic findings and taking into account the distribution of the disease. It has been stated that when a mucinous carcinoma is diagnosed in the ovary, further investigations, such as colonoscopy and detailed imaging of the upper abdomen, should be undertaken to exclude a primary neoplasm elsewhere but I feel this is unnecessary. Features suggesting a metastatic mucinous carcinoma in the ovary have been extensively discussed elsewhere<sup>46–52</sup> and are listed in Table 3.

**Table 3** Features favouring metastasis in ovarian mucinous carcinoma

Bilateral tumours
Small tumours
Nodular pattern of ovarian involvement
Microscopic surface deposits of tumour
Marked lymphovascular space invasion (especially outside ovary and in hilum)
Marked variation in growth pattern from one nodule to another
Destructive stromal invasion
Single cell infiltration and signet ring cells
Cells 'floating' in mucin
Extraovarian spread

None of these features are pathognomonic but are often seen in combination.

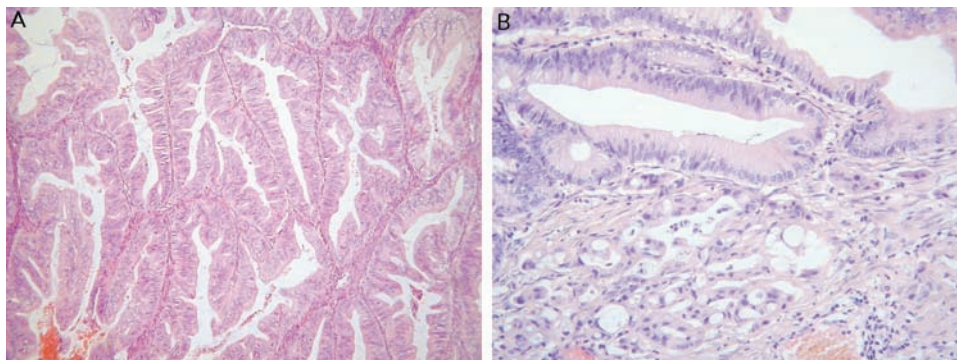
### Pathological features of primary ovarian mucinous carcinomas

Most primary ovarian mucinous carcinomas (and borderline tumours) are of so-called intestinal (enteric or non-specific) type. While many of these contain goblet cells, and even occasionally Paneth or neuroendocrine cells, the presence of goblet cells is not a prerequisite for an intestinal type mucinous tumour. In fact, with regard to their mucin histochemical profile, many of these more closely resemble gastric or pancreaticobiliary (upper gastrointestinal) mucinous neoplasms.<sup>67</sup> A much more uncommon müllerian (endocervical) type of ovarian mucinous carcinoma and borderline tumour also exists.<sup>68,69</sup> While borderline mucinous neoplasms of müllerian type are well described, malignant müllerian mucinous tumours are extremely uncommon and may, in the main, represent endometrioid carcinomas with marked accumulation of intracytoplasmic mucin;<sup>69</sup> given their rarity, they will not be discussed further in this review.

Primary ovarian mucinous carcinomas of intestinal type are usually large unilateral neoplasms with a smooth capsule and confined to the ovary at diagnosis (stage I). They are usually multiloculated, often with thick tenacious mucus. On sectioning, solid areas and foci of necrosis are commonly present; the solid and necrotic areas may histologically be borderline or malignant. Ovarian mucinous neoplasms of intestinal type comprise a spectrum or continuum from benign through borderline to malignant. In other words, intestinal type ovarian mucinous carcinomas, like low grade serous carcinomas, are thought to arise through a well defined adenoma-carcinoma sequence from a benign cystadenoma through a borderline tumour to a mucinous carcinoma.<sup>1,46–52</sup> Categories of intraepithelial carcinoma and microinvasion are also described. The designation intraepithelial carcinoma should be reserved for borderline tumours in which there is severe atypia of the epithelial lining.<sup>48</sup> Microinvasion is not uncommon in mucinous borderline tumours. The upper size limit has varied between studies but most use 5 mm (others use 3 mm or 10 mm<sup>2</sup>); multiple separate areas of microinvasion may occur. It is recommended that microinvasive areas are classified as borderline with microinvasion or microinvasive carcinoma.<sup>48</sup> The former is more common and is characterised by small groups or single morphologically bland cells, often with abundant eosinophilic cytoplasm, within the stroma. Cytokeratin stains sometimes highlight more invasive cells than can be appreciated on examination of the haematoxylin and eosin stained slides. Microinvasive carcinoma is characterised by the presence of a small invasive carcinoma with high grade

nuclear features, sometimes representing anaplastic carcinoma. The first pattern of microinvasion is not thought to have any influence on prognosis while microinvasive carcinoma may behave aggressively. Because of the continuum from benign to malignant, it is not uncommon to see an admixture of different morphological patterns (benign, borderline, borderline with intraepithelial carcinoma, microinvasion, carcinoma) side by side within an individual neoplasm. Given this heterogeneity, and the fact that primary ovarian intestinal type mucinous neoplasms are typically very large, extensive pathological sampling is mandatory to rule out a small focus of invasion which may potentially result in adverse behaviour. The degree of sampling necessary has been discussed previously<sup>1</sup> and it is generally recommended that one block per cm should be taken from tumours 10 cm or smaller and two blocks per cm of neoplasms larger than this. However, a degree of common sense should also be applied and areas which are solid or different in appearance should be preferentially sampled and if there are worrisome features in the initial sections, such as intraepithelial carcinoma or areas suspicious of invasion or microinvasion, additional sections should be examined.

Invasion in primary ovarian mucinous carcinomas can be either expansile (non-destructive or confluent glandular) or infiltrative (destructive) in type (Fig. 6);<sup>1,46–52,65,66</sup> the former is more common and is associated with a relatively good prognosis. The pattern of invasion should be detailed in the pathology report and sometimes the two types of invasion coexist. It may be difficult to diagnose a mucinous carcinoma with expansile invasion due to the orderly growth pattern and absence of a stromal reaction and, as discussed, this is an area where there is significant interobserver variability between pathologists. My criteria for the distinction between a borderline mucinous tumour and a carcinoma exhibiting expansile invasion are that the latter contain closely packed small to intermediate sized glands with a confluent back to back arrangement and no or minimal intervening stroma. A labyrinthine or cribriform growth pattern is also common.<sup>1</sup> This is analogous to the criteria used to diagnose a grade 1 endometrioid adenocarcinoma in the uterus where the diagnosis is made on the basis of a back to back architecture with stromal exclusion. Establishing a diagnosis of a mucinous carcinoma with infiltrative (destructive) stromal invasion is straightforward. Although this may occur, usually in association with expansile invasion, a secondary neoplasm should always be considered. Although there is no evidence base, the Royal College of Pathologists Ovarian Cancer Datasets in the United Kingdom recommend that primary ovarian mucinous carcinomas are graded in the



**Fig. 6** (A) Primary ovarian mucinous carcinomas exhibiting expansile and (B) a mixture of expansile (top) and infiltrative (bottom) stromal invasion.

same way as endometrioid carcinomas<sup>20</sup> (see later). Most primary ovarian mucinous carcinomas are well or moderately differentiated (grade 1 or 2) and confined to the ovary.

Occasionally, especially in the context of a borderline mucinous neoplasm, there is a sharp demarcation between a borderline area and a solid cellular area, a so-called mural nodule.<sup>70,71</sup> The mural nodules may be benign (either sarcoma-like composed of a mixture of osteoclast-like giant cells, inflammatory cells and mononuclear cells or corresponding to some specific benign neoplasm such as leiomyoma, rhabdomyoma or haemangioma) or malignant. The malignancy is most commonly anaplastic carcinoma but may be sarcoma or carcinosarcoma.<sup>70</sup> The anaplastic carcinoma may be composed of spindled, pleomorphic or rhabdoid cells.<sup>70</sup> It is likely that some previously reported examples of sarcoma-like mural nodules actually represent anaplastic spindle cell carcinoma and cyto-keratins stains may be useful in confirming this.

### Immunohistochemistry of primary ovarian mucinous carcinomas

As discussed, most primary ovarian mucinous carcinomas (and borderline tumours) are of so-called intestinal type. Intestinal type ovarian mucinous neoplasms are typically diffusely positive with CK7 but also commonly express, focally or diffusely, enteric markers such as CK20, CDX2, CEA and CA19.9 and are negative with hormone receptors, CA125 and WT1.<sup>72,73</sup> CA19.9 especially is often diffusely positive and there may be elevation of the serum level of this marker.<sup>74</sup> Serum CA19.9 levels may be extremely high and are of no value in predicting preoperatively whether an ovarian mucinous neoplasm is benign, borderline or malignant.<sup>74</sup>

### Molecular events in primary ovarian mucinous carcinomas

Similar to low grade serous carcinomas, ovarian mucinous tumours of intestinal type commonly exhibit k-ras mutations and identical mutations have been demonstrated in benign, borderline and malignant areas within the same neoplasm, suggesting that k-ras mutation is an early event in the evolution of these tumours.<sup>75-77</sup> Unlike low grade serous carcinomas, b-raf mutations are not a feature of ovarian mucinous neoplasms of intestinal type.

### Behaviour of primary ovarian mucinous carcinomas

As discussed previously, most primary ovarian mucinous carcinomas of intestinal type are unilateral and stage I. Advanced stage (stage III or IV) primary ovarian mucinous carcinomas are very rare and a secondary should always be excluded. The prognosis of stage I primary ovarian mucinous carcinoma is relatively good, although some cases recur, usually in the pelvis or abdomen; recurrence is associated with a poor prognosis. In one recent population-based study of 31 primary ovarian mucinous carcinomas, eight of 31 recurred.<sup>65</sup> Infiltrative stromal invasion is associated with a worse prognosis than expansile invasion. Advanced stage primary ovarian mucinous carcinomas have a dismal prognosis and respond poorly to the traditional chemotherapeutic agents used to treat ovarian carcinomas. However, it is again stressed that these are extremely uncommon. Malignant mural nodules are usually associated with a poor prognosis, although a recent study has shown that stage IA tumours with malignant mural nodules may be associated with a relatively favourable outcome.<sup>70</sup>

## ENDOMETRIOID ADENOCARCINOMA

Most, but not all, ovarian endometrioid adenocarcinomas are low grade and low stage (usually confined to the ovary, stage I). They are usually unilateral but approximately 10% are bilateral. They often, although not always, arise from endometriosis (especially an endometriotic cyst) or a pre-existing borderline adenofibroma.<sup>78,79</sup> The prevalence of primary ovarian endometrioid adenocarcinoma is lower in recent than in older studies.<sup>7,8</sup> This is almost certainly due to the recognition that many neoplasms which were previously diagnosed as high grade and high stage endometrioid carcinomas are, in fact, serous in type. This is an area where previously there was poor reproducibility amongst pathologists and where WT1 staining may be useful (discussed later). With an endometrioid adenocarcinoma involving the ovary, there is not uncommonly a synchronous endometrioid proliferation, either premalignant or malignant, within the uterine corpus.<sup>80</sup> If conservative management (unilateral salpingo-oophorectomy) is undertaken for a stage I ovarian endometrioid adenocarcinoma, the endometrium should be sampled to exclude significant pathology here.

Diagnosing a low grade endometrioid adenocarcinoma is usually straightforward, although problems may arise in the distinction between a grade 1 endometrioid adenocarcinoma and a borderline endometrioid adenofibroma.<sup>79</sup> Some low grade endometrioid adenocarcinomas exhibit obvious stromal invasion but in many (probably the majority) the diagnosis is made on the basis of a back-to-back glandular architecture with exclusion of stroma, similar to the criteria used to diagnose an endometrioid adenocarcinoma of the endometrium (Fig. 7). The presence of glandular confluence and a back-to-back architecture with stromal exclusion should result in a diagnosis of endometrioid adenocarcinoma even when the cytological features are low grade. The presence of one or more of the important triad of adenofibromatous areas, squamous elements (morular or non-morular) and endometriosis may be a useful pointer towards an endometrioid neoplasm. Unusual morphological features occasionally seen in ovarian endometrioid adenocarcinomas, either focally or diffusely, include sex cord-like formations and spindle cell differentiation; these features also occur more uncommonly in the corresponding uterine neoplasms.<sup>81</sup> The other morphological variants of uterine endometrioid adenocarcinoma, such as secretory and oxyphilic, may also occur in the ovary. High grade ovarian

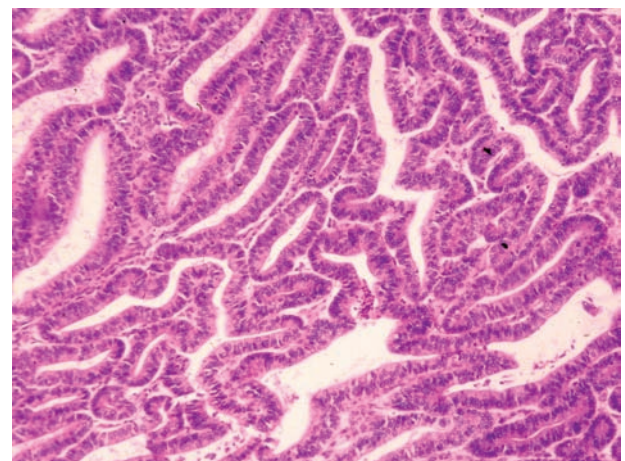


Fig. 7 Low grade endometrioid adenocarcinoma of ovary with back to back glandular arrangement.

**Table 4** Markers of use in distinction between ovarian endometrioid adenocarcinoma and colorectal adenocarcinoma

	Ovarian endometrioid adenocarcinoma	Colorectal adenocarcinoma
CK7	Diffusely positive	Negative
CK20	Negative	Diffusely positive
ER	Diffusely positive	Negative
CA125	Diffusely positive	Negative
CEA	Negative	Diffusely positive
CDX2	Negative or focally positive (squamous morules are positive)	Diffusely positive

endometrioid adenocarcinomas exist but are relatively uncommon. The distinction between a high grade endometrioid and a high grade serous carcinoma is discussed later. Endometrioid adenocarcinomas of the ovary are usually ER positive, negative with WT1, negative or patchily positive with p16 and exhibit 'wild-type' staining with p53. Occasionally there is an admixture of low grade (grade 1 or 2) endometrioid adenocarcinoma and undifferentiated carcinoma, so-called dedifferentiated endometrioid carcinoma (this is discussed later in the section on undifferentiated carcinoma).

Metastatic adenocarcinomas from several sites, especially the colorectum, may mimic a primary ovarian endometrioid adenocarcinoma.<sup>49–52</sup> Careful morphological examination (squamous elements, adenofibromatous areas or endometriosis suggesting an endometrioid adenocarcinoma; segmental or dirty necrosis or a garland-like growth pattern suggesting a colorectal adenocarcinoma) combined, if necessary, with immunohistochemistry facilitates the distinction. Differential cytokeratin (CK7 and CK20) staining is virtually diagnostic in the distinction between an endometrioid adenocarcinoma and a metastatic colorectal adenocarcinoma with a pseudoendometrioid appearance. Other markers which may assist include ER, CA125, CEA and CDX2 (Table 4).<sup>53–60</sup> The latter is an enteric marker which is diffusely positive in most colorectal adenocarcinomas but which on occasions is focally positive in ovarian endometrioid carcinomas (personal observations); squamous morules, which are common in endometrioid proliferations within the ovary and endometrium, are almost always CDX2 positive.<sup>82</sup>

In the Royal College of Pathologists Ovarian Cancer Dataset,<sup>20</sup> it is recommended that ovarian endometrioid adenocarcinomas are graded using the FIGO system used to grade uterine endometrioid adenocarcinomas. Although less extensively studied, endometrioid adenocarcinomas of the ovary exhibit similar molecular events to those seen in uterine endometrioid adenocarcinomas; these include PTEN,  $\beta$ -catenin, k-ras and PIK 3CA mutations and microsatellite instability.<sup>83</sup>  $\beta$ -catenin mutations are especially characteristic of low grade endometrioid adenocarcinomas with squamous morules.<sup>84</sup>

## CLEAR CELL CARCINOMA

Recent studies suggest that primary ovarian clear cell carcinomas occur with approximate equal frequency to endometrioid adenocarcinomas. Clear cell carcinomas are typically composed of cells with abundant clear cytoplasm, often with prominent cell membranes; an oxyphilic variant also exists.<sup>85</sup> The latter is usually a focal finding within an otherwise typical clear cell carcinoma but occasionally is the predominant or

exclusive element. Clear cell carcinomas have a characteristic morphological appearance typically consisting of an admixture of architectural arrangements including tubulocystic, glandular, solid and papillary (Fig. 8). Hobnail cells and eosinophilic stromal hyalinisation are common.<sup>85</sup> A plasmacytic or neutrophilic infiltrate may be present. Some have a low power architecture which closely mimics a serous borderline tumour.<sup>86</sup> On occasions, a component of benign or borderline clear cell adenofibroma is identified, although it may be difficult to ascertain whether this represents a precursor lesion or merely a growth pattern in a clear cell carcinoma. It is the admixture of architectural patterns which is more characteristic of clear cell carcinoma than the presence of clear cells *per se* since clear cells are sometimes a feature of both serous and endometrioid carcinomas. In the absence of the architectural features listed, a diagnosis of clear cell carcinoma should be doubted.<sup>85</sup> Most clear cell carcinomas are diagnosed at early stage (stage I or II) and the majority arise in endometriosis. Careful pathological sampling, especially concentrating on cystic areas, will usually reveal background endometriosis, often in the form of an endometriotic cyst.

Most authorities recommend that ovarian clear cell carcinomas are automatically graded as grade 3.<sup>20</sup> Since these neoplasms are often architecturally well differentiated, sometimes have a relatively low cytological grade and are typically mitotically quite inactive (average 3–4 mitoses per 10 high power fields<sup>85</sup>), formal grading using one of the universal systems may result in these being categorised as grade 1 or 2. Clear cell carcinomas are usually negative with ER, WT1 and p53 (so-called 'triple negative'). They are usually negative or focally positive with p16.

It is widely assumed that clear cell carcinomas have a relatively poor prognosis. However, the prognosis of stage I ovarian clear cell carcinomas is relatively good. Advanced stage clear cell carcinomas have a poor prognosis and appear relatively resistant to the traditional chemotherapeutic agents used in the treatment of ovarian carcinoma; it is possible that this is because these neoplasms exhibit a low proliferation index.

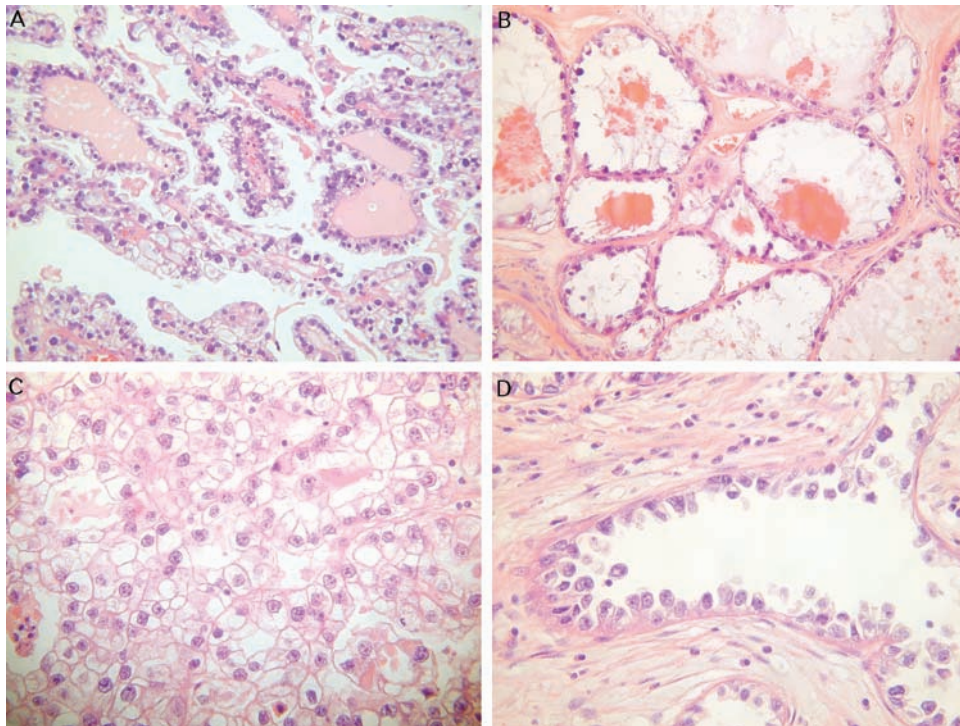
The underlying molecular events in ovarian clear cell carcinoma have not been extensively investigated<sup>87</sup> but a recent study identified ARID1A mutations in a significant percentage of cases.<sup>88</sup>

## TRANSITIONAL CARCINOMA

In my opinion, primary ovarian transitional carcinomas are rare, although they do exist.<sup>89</sup> I feel most tumours which are diagnosed as transitional carcinoma represent variants of high grade serous carcinoma and that transitional carcinoma is a poorly reproducible diagnosis. Other tumours diagnosed as transitional carcinoma may represent endometrioid adenocarcinomas with a transitional-like growth pattern. Transitional carcinomas of the ovary express müllerian and not urothelial markers and are usually positive with WT1,<sup>90</sup> a point in favour of many being variants of high grade serous carcinoma. Some recur or metastasise as high grade serous carcinoma and this is further evidence that many are variants of the latter.

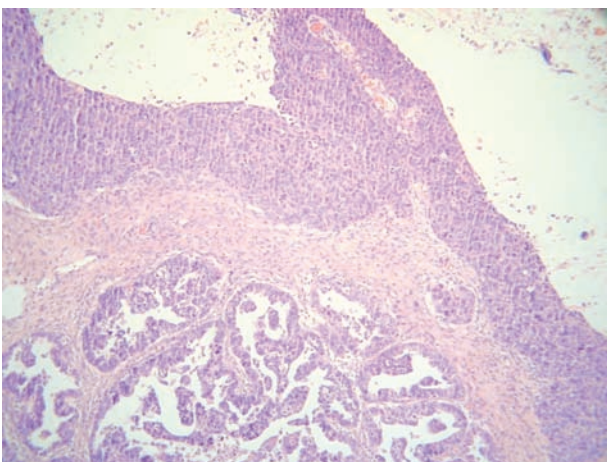
## UNDIFFERENTIATED CARCINOMA

The WHO definition of an undifferentiated ovarian carcinoma is a primary ovarian carcinoma with no differentiation or only small foci of differentiation.<sup>6</sup> These are uncommon but not rare



**Fig. 8** Ovarian clear cell carcinoma with (A) papillary, (B) tubulocystic and (C) solid growth patterns and (D) hobnail cells.

and most probably represent the extreme end of the spectrum of high grade serous carcinoma since undifferentiated areas are not uncommonly seen in the latter. With a seemingly undifferentiated ovarian carcinoma, further sampling may reveal areas more diagnostic of high grade serous carcinoma, such as vague papillary formations, slit-like spaces or psammoma bodies (Fig. 9). Global gene expression studies support the hypothesis that most undifferentiated ovarian carcinomas are related to high grade serous carcinoma.<sup>3</sup> WT1 staining also supports this since many, but not all, undifferentiated ovarian carcinomas exhibit nuclear staining with this marker which is commonly expressed in ovarian serous carcinoma.<sup>1,3</sup> A smaller number of undifferentiated ovarian carcinomas may represent dedifferentiation within a low grade endometrioid adenocarcinoma; the concept of dedifferentiation within uterine and ovarian



**Fig. 9** Largely undifferentiated ovarian carcinoma (top) where foci with a papillary architecture are present in keeping with high grade serous carcinoma (bottom).

endometrioid adenocarcinomas, especially the former, has been highlighted in recent years.<sup>91</sup>

### MIXED CARCINOMAS

According to the WHO, a mixed carcinoma should only be diagnosed when the minor component makes up at least 10% of the neoplasm.<sup>6</sup> However, all morphological subtypes within an ovarian carcinoma should be documented and the percentages listed, even if the minor component accounts for less than 10%. True mixed carcinomas of the ovary (unlike in the uterus) are relatively uncommon, although they do occur.<sup>1-4</sup> A combination of endometrioid and clear cell carcinoma occasionally occurs since both tumour types commonly arise in endometriosis. Neoplasms which are diagnosed as mixed serous and endometrioid or mixed serous and clear cell carcinoma mostly represent high grade serous carcinomas with areas which mimic endometrioid or clear cell carcinoma; the combination of serous and endometrioid or serous and clear cell carcinoma is uncommon. This is discussed further in the next section. The combinations of serous and undifferentiated or endometrioid and undifferentiated carcinoma have already been discussed. The former should be reported as a high grade serous carcinoma with a comment that undifferentiated areas are present and that this is in keeping with the spectrum of high grade serous carcinoma.

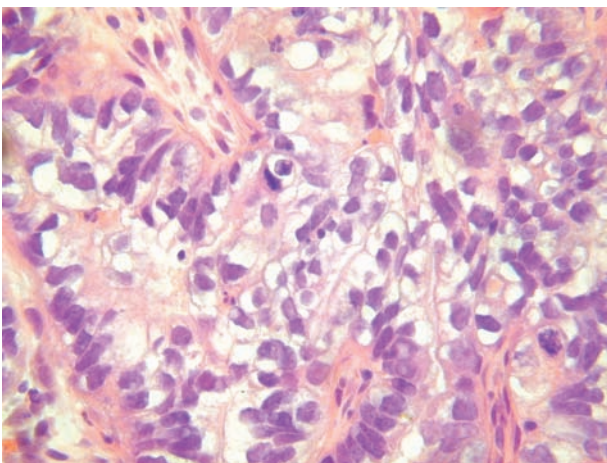
### PROBLEMATIC AREAS IN TYPING OF OVARIAN CARCINOMAS

There are problems with regard to typing some poorly differentiated ovarian carcinomas. The situation has improved over the past few years and a recent study has shown that when using modern diagnostic criteria, excellent interobserver agreement can be achieved amongst specialist gynaecological and general pathologists in the typing of ovarian carcinomas.<sup>92</sup> In fact, the

situation is much better with ovarian than uterine carcinomas where considerable problems still exist in the categorisation of high grade carcinomas. Many of the difficulties in classification of ovarian carcinomas relate to the categories of high grade serous, high grade endometrioid and undifferentiated carcinoma in which there is morphological overlap. Another problematic area is the categorisation of clear cell areas within an ovarian carcinoma, specifically whether these represent a clear cell carcinoma or component of clear cell carcinoma or clear cells within a serous, endometrioid or undifferentiated carcinoma.

Previously some pathologists tended to diagnose many poorly differentiated ovarian carcinomas as serous in type, while others classified them as endometrioid or mixed serous and endometrioid. The prevailing view, and my personal opinion, is that the vast majority represent high grade serous carcinomas. In this distinction, WT1 immunohistochemical staining may be of value.<sup>93–96</sup> Most (80–90%) primary ovarian (as well as primary peritoneal and tubal) serous carcinomas exhibit diffuse nuclear positivity with WT1 while most endometrioid adenocarcinomas are negative or at the most focally positive.<sup>93–96</sup> In problematic cases, WT1 staining is recommended as an adjunct to help distinguish between a high grade serous and a high grade endometrioid adenocarcinoma. As discussed, most undifferentiated ovarian carcinomas represent the extreme end of the spectrum of high grade serous carcinoma and WT1 staining may be useful in this regard. There is now a widely held view that most high grade serous and undifferentiated carcinomas, and what some report as high grade endometrioid carcinomas, represent variants of high grade serous carcinoma; this is supported by global gene expression studies which cannot distinguish these at a molecular level.<sup>3</sup>

Characteristically in ovarian clear cell carcinoma, an admixture of growth patterns is present, as discussed previously.<sup>85</sup> Most clear cell carcinomas are diagnosed without difficulty but there is a tendency to overdiagnose clear cell carcinoma or a clear cell carcinoma component due to the presence of clear cells within serous (Fig. 10) and to a lesser extent endometrioid adenocarcinomas. The presence of areas of more typical serous or endometrioid adenocarcinoma are useful pointers in diagnosis (as discussed, sometimes a combination of clear cell and endometrioid carcinoma occurs) and it is stressed that the mere presence of clear cells does not constitute a clear cell carcinoma. WT1, ER and p53 are usually negative in ovarian clear cell carcinoma; as discussed, most high grade serous



**Fig. 10** High grade serous carcinoma of ovary containing cells with clear cytoplasm resulting in potential for misdiagnosis as clear cell carcinoma.

carcinomas are positive with these markers while most endometrioid carcinomas are ER positive. Recently, hepatocyte nuclear factor 1 beta has been shown to be a promising nuclear marker of ovarian (and uterine) clear cell carcinomas,<sup>97,98</sup> although further studies are needed to more fully evaluate the full range of immunoreactivity with this marker.

## CONCEPT OF TYPE I AND TYPE II OVARIAN CARCINOMA

Given the major recent advances in our knowledge regarding the pathogenesis, natural history and behaviour of the major subtypes of ovarian carcinomas, we can now think of a broad dualistic pathway of ovarian epithelial carcinogenesis; similar to the uterus, the terms type I and type II ovarian carcinomas have been proposed.<sup>2</sup> This does not imply that the terms type I and type II carcinoma should replace the specific histological subtypes but, like the dualistic pathway relating to the pathogenesis of uterine carcinomas, this terminology is concerned with broad mechanisms of tumour development. Type I tumours are considered to arise via a well defined adenoma-carcinoma sequence from a benign precursor lesion, such as a borderline tumour or endometriosis, and to evolve in a stepwise fashion. They are associated with a variety of molecular events, as discussed earlier. Type I tumours are, in general, slow growing and indolent neoplasms and include low grade serous, endometrioid, mucinous and clear cell carcinoma and malignant Brenner tumour. There are obvious parallels with type I endometrial cancers which are also, in general, indolent and arise from a well defined precursor, atypical hyperplasia. In contrast, type II ovarian carcinomas are high grade clinically aggressive neoplasms. Most represent high grade serous carcinoma. Carcinosarcoma (similar to the situation in the uterine corpus, most ovarian examples represent high grade serous carcinomas with sarcomatous elements which derive from the epithelial malignancy<sup>99,100</sup>) and undifferentiated carcinoma, which are both predominantly variants of high grade serous carcinoma, are also included in this category. Type II carcinomas are often associated with TP53 mutations and there is emerging evidence that many arise from the epithelium of the distal fallopian tube. Again there are obvious parallels with type II endometrial cancers. In rare cases, a type I carcinoma can transform into a type II, as discussed earlier.

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