Ovarian Carcinoma: Recent Developments in Classification of Tumour Histological Subtype

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ABSTRACT

Histological types of ovarian carcinomas are distinct entities with different molecular and immunohistochemical profiles and clinical outcomes. The implementation of subtype-specific therapies for subtypes of ovarian cancer requires reproducible histological diagnoses. More than 95% of ovarian carcinomas can be reproducibly diagnosed as one of five histological types, in descending order of frequency: high-grade serous carcinoma, clear cell carcinoma, endometrioid carcinoma, mucinous carcinoma, and low-grade serous carcinoma. There are occasional cases of mixed histological type, and rare cases defy classification (adenocarcinoma not otherwise specified [NOS], or unclassifiable). Although immunohistochemical markers are a useful adjunct for the assignment of histological type, by using the modified definitions presented in this review, the majority of ovarian carcinomas can be reliably assigned to a category without recourse to immunohistochemistry.

RÉSUMÉ

En vertu de leur classification histopathologique, les carcinomes ovariens se distinguent par leurs caractéristiques moléculaires et immunohistochimiques particulières et par leur issue clinique. Le diagnostic histologique reproductible est essentiel à la planification d'un traitement conçu en fonction du sous-type précis de cancer ovarien. Il est possible d'établir le diagnostic reproductible de 95 % des carcinomes ovariens selon l'une ou l'autre des cinq formes histologiques que voici (par ordre décroissant de fréquence) : le cystadénocarcinome séreux de haut degré de malignité, le carcinome à cellules claires, le carcinome endométrioïde, le cystadénocarcinome mucineux et le cystadénocarcinome séreux de faible degré de malignité. Parfois, il s'agit d'une forme histologique mixte ou, dans de rares cas, d'une forme qui échappe à la classification (adénocarcinome sans autre précision ou inclassable). Bien que les marqueurs immunohistochimiques soient utiles dans la détermination de la forme histologique, la majorité des carcinomes ovariens peuvent être classés avec fiabilité dans l'une ou l'autre des catégories histopathologiques sans le recours à l'immunohistochimie grâce aux définitions modifiées présentées ici.

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This article has been peer reviewed.

Competing interests: Dr. Gilks received an honorarium ($2,000) from Roche Pharmaceuticals to participate on a review panel in 2010.

Ovarian cancer is not a single disease but comprises more than 15 distinct tumour types classified according to histological appearance.[1] Increasingly, subtype-specific risk factors (environmental and genetic), molecular events, prognostic markers, and therapeutic targets are being identified, and histological type is an important surrogate for underlying molecular aberrations.[2] Thus, designation of an individual tumour as a specific histological type conveys genetic, prognostic, and, increasingly, predictive information about response to treatment. There is also growing recognition of the need for histological type-specific clinical trials, with clear cell carcinoma and mucinous carcinoma often demonstrating resistance to current chemotherapy regimens.[3] These issues mandate accurate and reproducible assessment of histological type by pathologists.

In this review, we will focus on recent areas of refinement in the diagnosis of malignant surface epithelial tumours, which are the most common ovarian cancers, accounting for 90% of cases, and are the most lethal gynecological malignancies. The five principal subtypes of surface epithelial carcinomas are (1) high-grade serous carcinoma, (2) endometrioid carcinoma, (3) mucinous carcinoma, (4) clear cell carcinoma, and (5) low-grade serous carcinoma (Figure 1). The last is a distinct disease type and not part of a morphological continuum with high-grade serous carcinoma. We regard transitional carcinoma as a variant of high-grade serous carcinoma, as it has been shown, on the basis of immunohistochemical and molecular evidence, to be indistinguishable from conventional high-grade serous carcinoma. These five subtypes account for more than 97% of cases of ovarian surface epithelial carcinoma.[4]

Reproducibility of Histological Diagnosis

Studies of reproducibility of the 1973 World Health Organization (WHO) classification of ovarian carcinoma, based on histological type, consistently showed moderate levels of interobserver reproducibility, with concordance rates of 56% to 68% and kappa statistics of 0.46 to 0.55.[5–9] The consistently problematic areas identified in these studies included histological type assignment for high-grade carcinoma (especially high-grade endometrioid carcinoma versus high-grade serous carcinoma), undifferentiated histological types versus specifically differentiated histological types, and mixed histological types versus pure histological types. The problem has persisted, as demonstrated by the diverse diagnoses made by expert pathologists for a series of ovarian carcinomas; this was highlighted at the International Society of Gynecological Pathologists companion society meeting at the 2007 U.S. and Canadian Academy of Pathology meeting.

Recent refinements in morphological criteria attained through detailed follow-up studies of large ovarian cancer cohorts, coupled with immunohistochemical biomarker profiling, have allowed more reproducible diagnoses of histological types. Particular areas of clarification include distinguishing between high-grade serous carcinoma and endometrioid carcinoma[10,11]; mixed histological type and pure histological type (particularly mixed serous carcinoma and clear cell carcinoma)[12]; undifferentiated histological types and specifically differentiated histological types; and high-grade and low-grade serous carcinoma.[13,14] Using these contemporary histopathological criteria, we showed in a trans-Canadian study that histological-type diagnosis is now much more reproducible (kappa = 0.89).[15]

Role of Grading in Ovarian Carcinoma

In addition to histological type assessment, ovarian cancers have been graded, with the exception of clear cell carcinoma and undifferentiated carcinomas. The grade of the carcinoma was formerly thought to have prognostic significance that was exceeded only by the stage of the carcinoma. Several grading systems of ovarian cancer are currently in use, including histotype-specific systems as well as universal grading systems, which are applicable to all histological types of ovarian cancer.[16] Although the International Federation of Gynecology and Obstetrics (FIGO) grading system is based predominantly on tumour architecture, the Silverberg system assesses architecture, nuclear atypia, and mitotic index. Grade has not been shown to be a significant prognostic indicator independent of tumour histological type in cases where careful assessment of histological type has been made by using current diagnostic criteria.[11,17] Thus, within the groups of high-grade serous, low-grade serous, mucinous, clear cell, and endometrioid carcinomas, grade does not convey prognostic information. Grade is used for making the important

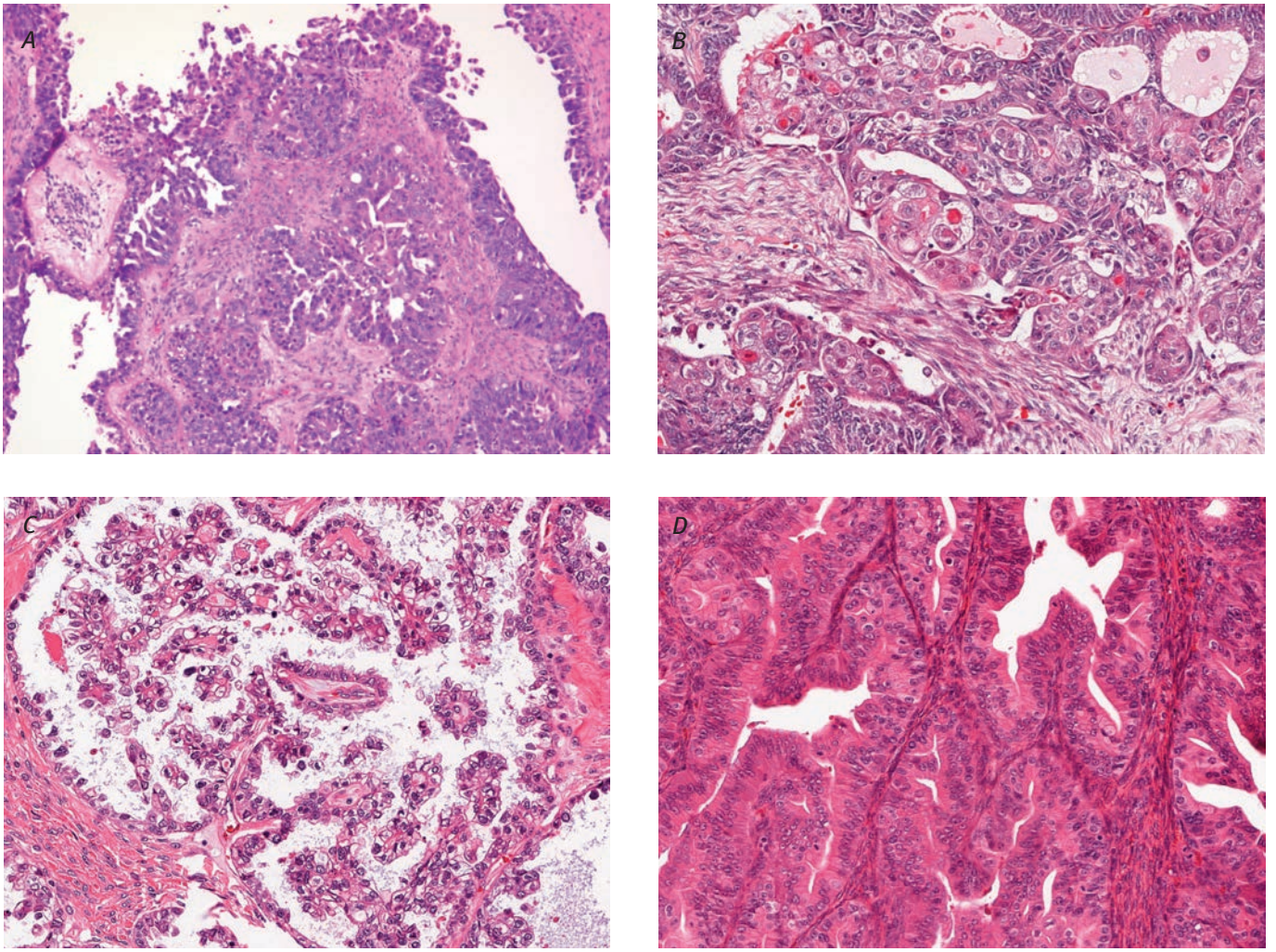

Figure 1. The five subtypes of ovarian carcinoma: *A*, High-grade serous carcinoma. *B*, Endometrioid carcinoma. *C*, Clear cell carcinoma. *D*, Mucinous carcinoma. *E*, Low-grade serous carcinoma. (Hematoxylin and eosin)

distinction between low-grade serous carcinoma and high-grade serous carcinoma and, for this purpose, is highly reproducible;[13,14] however, it is not otherwise a sufficiently reliable basis for individual treatment recommendations. Overall, grade is still poorly reproducible with the kappa statistic ranging from 0.27 to 0.64, depending on the grading system used. With reproducible diagnoses, the future direction will be to identify additional histopathological features or biomarkers that are reproducible and can be used for prognostication and prediction of therapeutic response.

WHO Criteria

The 2003 WHO criteria are similar to the earlier 1973 criteria in that they are general and descriptive.[1] They did not include any changes that would be expected to improve the reproducibility of diagnoses. These criteria are presented below:

1. *Serous carcinoma:* "composed of cells ranging in appearance from those resembling fallopian tube epithelium in well-differentiated tumours to anaplastic epithelial cells with severe nuclear atypia in poorly differentiated tumours"
2. *Mucinous carcinoma:* "in its better differentiated areas resembles intestinal or endocervical epithelium"
3. *Endometrioid carcinoma:* "closely resembles the common variant of endometrioid carcinoma of the uterine corpus"
4. *Clear cell carcinoma:* "composed of glycogen-containing clear cells and hobnail cells and occasionally other histological types"
5. *Transitional cell carcinoma:* "composed of epithelial elements histologically resembling malignant urothelial neoplasms and does not have a component of benign or borderline Brenner tumour"
6. *Undifferentiated carcinoma:* "a primary ovarian carcinoma with no differentiation or only small foci of differentiation"
7. *Unclassified adenocarcinoma:* "a primary ovarian adenocarcinoma that cannot be classified as one of the specific types of Müllerian adenocarcinoma"
8. *Mixed surface epithelial carcinomas:* "composed of an admixture of two or more of the five major histological types," and the minor component(s) "must comprise alone or together at least 10% of the tumour"

There have been significant advances in the histopathological diagnosis of ovarian carcinoma since these criteria were published, which has resulted in the simplification of the classification system so that a large majority of cases can be placed in one of five categories (see Figure 1); this has led to a dramatic reduction in the number of mixed tumours. In this review, we will specifically address areas where recent developments can help the pathologist arrive at the correct diagnosis.

High-Grade Serous Carcinoma versus Undifferentiated Carcinoma

High-grade serous carcinoma can have a protean morphology, with the most distinctive growth pattern consisting of stratified epithelium with a fenestrated appearance and slit-like spaces. The tumour cells are pleomorphic, intermediate to large in size, with scattered bizarre mononuclear giant cells; prominent nucleoli are common, and the mitotic rate is very high (Figure 2). Tumours with typical serous areas frequently show foci of solid growth (see Figure 2). Such tumours are not true mixed carcinomas and are best classified as high-grade serous carcinoma rather than mixed serous carcinoma or undifferentiated carcinoma. High-grade serous carcinomas, with or without a solid growth pattern, do not differ with respect to genetic risk factors (e.g., *BRCA* mutations), molecular abnormalities, or immunophenotype.

The category of undifferentiated carcinoma, whether as pure carcinoma or a component of mixed carcinoma, does exist, but such tumours are rare. Tumours with an undifferentiated pattern arising from a low-grade component, for example, a mural nodule of undifferentiated carcinoma arising in a mucinous carcinoma or low-grade endometrioid carcinoma associated with a de-differentiated component, are distinctive and rare variants of ovarian carcinoma and should be specifically noted as such in pathology reports.[18,19] Only tumours with an undifferentiated pattern throughout should be diagnosed as undifferentiated carcinoma; this is very rare when the tumour is well sampled. With a small biopsy specimen, serous-type architecture may not be appreciated. If such a tumour is WT-1 positive on immunostaining, it is most probably a high-grade serous carcinoma and can be signed out as poorly differentiated carcinoma, consistent with high-grade serous carcinoma.[20]

Serous Carcinoma versus Endometrioid Carcinoma

Most ovarian carcinomas, which used to be diagnosed as high-grade endometrioid carcinomas in the past, are indistinguishable from high-grade serous carcinomas on the basis of gene expression or immunostaining profiles.[2] They are also readily separable from the lower-grade (grade 1 or 2) endometrioid carcinomas of the ovary on the basis of

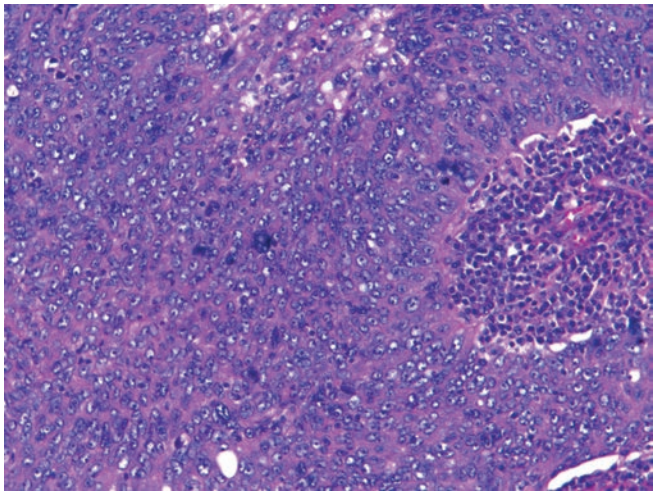

Figure 2. High-grade serous carcinoma: solid growth pattern and high grade nuclear features. (Hematoxylin and eosin)

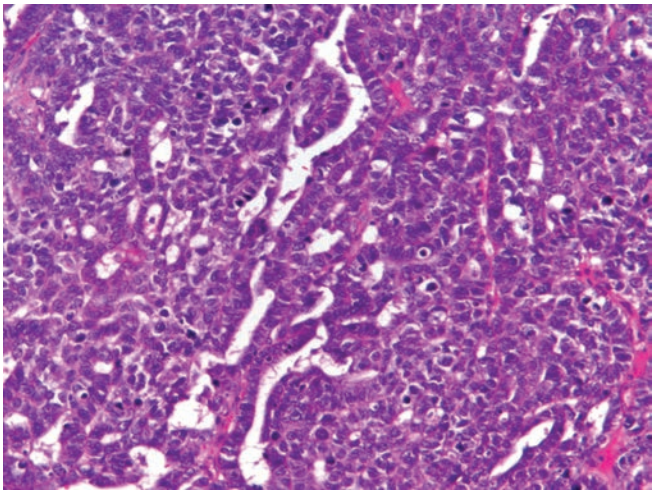

Figure 3. Glandular architecture in a high-grade serous carcinoma. (Hematoxylin and eosin)

morphology, gene expression, immunostaining profile, correlation with *BRCA* mutations (present in high-grade tumours), and lack of association with synchronous low-grade endometrioid carcinoma of the endometrium (present in up to 20% of low-grade endometrioid carcinomas of the ovary). This was illustrated in our retrospective review of more than 500 cases of ovarian carcinoma.[11] For this review, which was based on hematoxylin and eosin (H&E)–stained slides alone, we adopted a conservative interpretation of the WHO definition of endometrioid carcinoma, that is, a tumour that "closely resembles the common variant of endometrioid carcinoma of the uterine corpus." Of the 176 cases previously diagnosed as endometrioid, the diagnosis remained as such after review for 119, with 50 being reclassified as high-grade serous carcinoma. Reclassification of these 50 tumours was subsequently supported by immunohistochemistry, with 68.2% expressing WT-1, a marker of serous differentiation. This was not significantly different from the frequency of WT-1 positivity in the group of serous carcinomas as a whole (162 of 208; 77.8%) but was significantly higher than the frequency of WT-1 positivity in the tumours classified as endometrioid (5 of 129; 3.9%). It is now appreciated that serous carcinomas can have prominent glandular differentiation (Figure 3). In such cases, the high-grade cytological features, with nuclear pleomorphism and a high mitotic rate, can be the key to diagnosis, with immunostaining reserved for problematic cases. High-grade endometrioid carcinomas are rare, but they do exist; these tumours are indistinguishable from FIGO grade 3 carcinomas of the endometrium, showing a solid or near-solid growth admixed with well-formed glands. Association with squamous differentiation, a low-grade endometrioid component, or endometriosis is helpful in establishing the diagnosis. In our review, the percentage of ovarian endometrioid carcinomas that were grade 3 was 7% of all endometrioid carcinomas of the ovary, identical to the frequency of endometrial carcinomas of the endometrioid type of that grade.[11]

High-Grade Serous Carcinoma with Clear Cell Change versus Clear Cell Carcinoma

In British Columbia, clear cell carcinomas account for 12% of cases of ovarian carcinoma. Clear cell carcinoma is strongly associated with endometriosis and may be found in continuity with atypical endometriosis in an endometriotic cyst. Most clear cell carcinomas are stage I or II at diagnosis, and, unlike high-grade serous carcinomas, they do not show an association with germline or somatic *BRCA* mutations. Clear cell carcinoma overlaps morphologically with high-grade serous carcinoma owing to the frequent presence of papillary and solid architecture and high nuclear grade. The difference lies in the lower mitotic rate and hyalinized papillary cores in clear cell

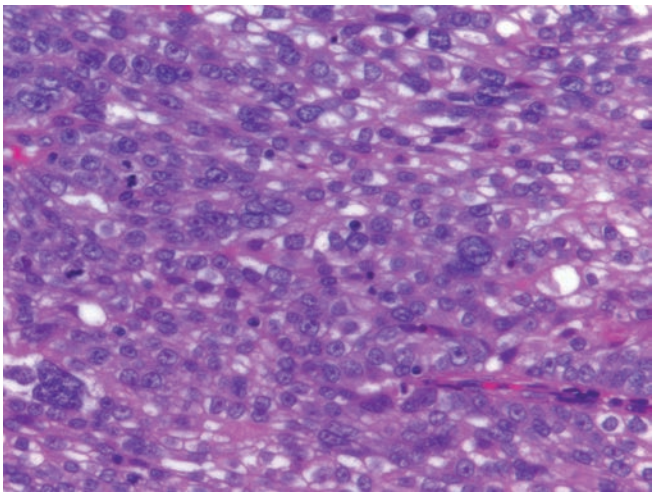

Figure 4. High-grade serous carcinoma with clear cell change. Elsewhere, this tumour, which was immunoreactive for both WT1 and ER, showed typical high-grade serous morphology. (Hematoxylin and eosin)

carcinoma, with less stratification of the overlying epithelial cells. Reproducibility of the diagnosis of mixed carcinomas with clear cell and high-grade serous components is particularly poor. We compared cases of pure clear cell carcinoma and pure high-grade serous carcinoma with cases diagnosed as mixed carcinomas with serous and clear cell components.[12] On the basis of high clinical stage at presentation and pathological features (high mitotic rate, expression of WT1, and ER), these so-called mixed tumours are significantly different from pure clear cell carcinoma and indistinguishable from pure high-grade serous carcinoma. The diagnosis of "high-grade serous carcinoma with clear cell change" is appropriate in these cases (Figure 4). We have not seen a convincing example of mixed serous and clear cell carcinoma and believe that such diagnosis is best avoided.

The differential diagnosis of clear cell carcinoma and high-grade serous carcinoma can be challenging to such an extent, especially with a small biopsy specimen, that immunostaining is required. We compared the immunophenotype of more than 200 clear cell carcinomas to a similar number of high-grade serous carcinomas, using a panel of three immunohistochemical markers: WT1, ER, and HNF-1β.[21] Most tumours (71%) showed either a typical clear cell carcinoma immunophenotype (WT1 and ER negative, HNF-1β positive) or a typical high-grade serous carcinoma immunophenotype (WT1 and ER positive, HNF-1β negative), and in these cases the diagnostic accuracy of the immunostaining approached 100%. Only 13% of cases had a completely uninformative immunophenotype with all markers being negative. In the other cases, immunostaining strongly supported either clear cell carcinoma (i.e., WT1 negative; ER and HNF-1β positive) or high-grade serous carcinoma (i.e., WT1 and HNF-1β negative; ER positive).

Clear Cell Carcinoma versus Serous Borderline Tumour

Diagnostic difficulties with clear cell carcinoma relate to its varied morphology and relative rarity. Recently Sangoi and colleagues highlighted a subset of clear cell carcinomas where the predominantly papillary architecture, low mitotic index, deceptively bland cytology, psammoma bodies, and comparatively inconspicuous hobnail cells led to confusion with serous borderline tumour, particularly when only a few sections of the tumour were examined.[22] In addition, most of the cases featured detached tumour cell clusters within cyst lumina that, together with the occasionally prominent cytoplasmic eosinophilia, simulated the epithelial tufting and eosinophilic cells characteristic of serous borderline tumour. Ovarian or pelvic endometriosis, hyalinized connective tissue cores, and clear cells were also present, although the clear cells were often subtle. The most helpful clue that helped arrive at a correct diagnosis was the presence of other patterns of clear cell carcinoma within the same tumour. Unfortunately, with a small biopsy or on frozen section, the limited sampling may not show the more characteristic areas of clear cell carcinoma. Although the data available are insufficient, it appears that the immunopanel used to distinguish high-grade serous carcinoma from clear cell carcinoma (i.e., WT1, ER, and HNF-1β) can serve to distinguish serous borderline tumour from clear cell carcinoma.

High-Grade Serous Carcinoma versus Low-Grade Serous Carcinoma

There is compelling evidence to support the separation of serous carcinomas into distinct low- and high-grade tumour types and not to regard them as part of a continuum of serous neoplasia.[13,14,23,24] Low-grade serous carcinomas are

characterized by distinct molecular alterations and clinical behaviour and can thus be reproducibly distinguished from high-grade serous carcinomas in clinical practice. For example, *BRAF* or *KRAS* mutations are present in most low-grade serous carcinomas and serous borderline tumours but not in high-grade serous carcinomas. Low-grade serous carcinomas do not show chromosomal instability and lack the complex genetic abnormalities seen in high-grade serous carcinomas. Low-grade serous carcinomas are not associated with *BRCA* germline mutations. Interestingly, low-grade serous carcinomas often present at high stage, similar to high-grade serous carcinomas and unlike clear cell, endometrioid, or mucinous carcinomas.[4] In British Columbia, low-grade serous carcinomas account for less than 3% of cases of ovarian carcinomas.

Low-grade serous carcinomas have uniform nuclei and differentiated architecture with papillary growth; numerous psammoma bodies are a common feature. The uniformity of the nuclei is the principal criterion for distinguishing between low-grade serous carcinoma and high-grade serous carcinoma, with less than three-fold variability in size (Figure 5). In cases where the application of this criterion is problematic, mitotic figures should be counted; the mitotic count in low-grade serous carcinoma is less than 13 per 10 high-power fields. These criteria have recently been shown to be highly reproducible. The cells of low-grade serous carcinoma may have prominent nucleoli, and this is not a criterion for distinction from high-grade serous carcinoma. Low-grade serous carcinoma can progress to high-grade carcinoma, but this is rare.[25] Low-grade serous carcinomas correspond to grade 1 serous carcinomas in the Silverberg grading system, whereas high-grade serous carcinomas are grade 2 or 3. As noted previously, there is no prognostic significance to grade 2 versus grade 3, and thus it is not necessary to make this distinction.

Immunohistochemistry is rarely needed in distinguishing between high-grade serous carcinoma and low-grade serous carcinoma. Generally, low-grade serous carcinomas show focal expression of p53 (i.e., with less than 20% of tumour cell nuclei staining), and p16 and a low Ki-67 index. High-grade serous carcinomas show either strong diffuse p53 expression or complete absence of p53, as well as strong diffuse p16 expression, with a high Ki-67 index.[26–28]

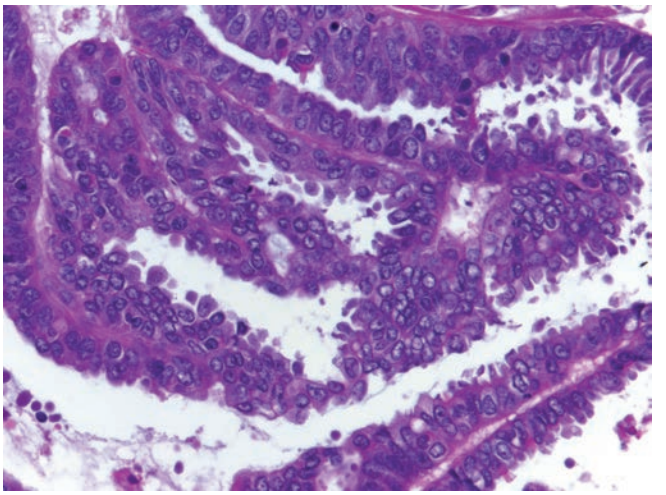

Figure 5. Uniform cytological features of low-grade serous carcinoma, with less than threefold variation in nuclear size. (Hematoxylin and eosin)

Although the mean Ki-67 proliferation indices are significantly different between low-grade and high-grade serous carcinomas (23% vs. 55%), 14% of low-grade serous carcinomas showed a proliferation index of greater than 50%. With regard to p16, in one study, 27% and 83% of low-grade and high-grade serous carcinomas, respectively, showed greater than 75% positive cells, whereas 50% of low-grade serous carcinomas and 8% of high-grade serous carcinomas showed 0% to 25% of cells staining.[26] Thus, although staining profiles differ, caution is needed in interpreting immunostaining results in individual cases.

Mixed Carcinoma

The category of mixed carcinomas, where more than one histological type coexists in an individual tumour, accounts for less than 5% of cases of ovarian carcinoma.[11] The most common combination in the review of cases from British Columbia was mixed clear cell–endometrioid carcinoma, and the morphological diagnosis was straightforward. In contrast, the second largest group of mixed carcinomas, with a high-grade serous–endometrioid component, included cases with a morphologically ambiguous pattern and intermediate features rather than clearly identifiable distinct components. The diagnostic criteria for this subgroup need further development, but they undoubtedly exist, just as they do in

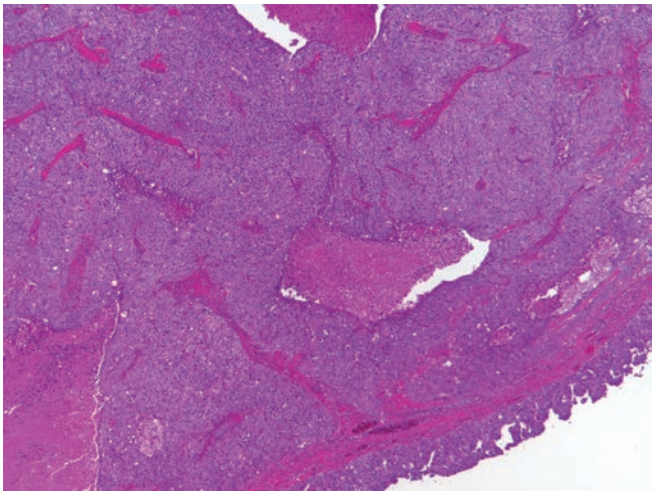

Figure 6. High-grade serous carcinoma with transitional-like growth: more typical high-grade serous architecture can be seen at the lower right. (Hematoxylin and eosin)

the endometrium; they are, however, likely to be rare. The third largest group, mixed endometrioid–mucinous carcinomas, can be considered analogous to endometrial–endometrioid carcinomas with mucinous differentiation; these low-grade carcinomas are not admixtures of endometrioid carcinoma and mucinous carcinoma of intestinal type but are variants of endometrioid carcinoma and should not be considered mixed carcinomas. Mixtures of undifferentiated carcinoma and mucinous or low-grade endometrioid carcinoma, both of which are rare, were discussed previously.

High-Grade Serous Carcinoma versus Transitional Cell Carcinoma

Transitional cell carcinomas without a Brenner component vary in frequency in different case series and cannot be reproducibly distinguished from high-grade serous carcinomas on histological grounds (Figure 6). Those tumours diagnosed as transitional cell carcinoma are also indistinguishable from high-grade serous carcinomas on the basis of immunostaining or molecular analysis.[29–31] Malignant Brenner tumours, that is, those carcinomas admixed with a benign or borderline component, are rare. Their immunophenotype (negative for ER and WT1, without p53 overexpression; R. Ali and B. Gilks, unpublished data) is different from that of transitional cell carcinoma–high-grade serous carcinoma, and it is unlikely that there is any relationship between those cases diagnosed as transitional cell carcinoma and those diagnosed as Brenner tumours. On the basis of the available evidence, transitional cell carcinomas are best considered a variant of high-grade serous carcinoma (high-grade serous carcinoma with transitional cell features), analogous to serous carcinoma with clear cell change. In some series, the cases diagnosed as transitional cell carcinoma have had a more favourable prognosis than high-grade serous carcinoma NOS, however, this has not been a consistent finding, and these tumours with transitional-like growth are not considered a clinically significant subset of high-grade serous carcinomas at the present time.[32]

Prediction of Ovarian Carcinoma Subtype

Examination of H&E-stained sections is usually sufficient to accurately and reproducibly classify ovarian carcinomas. In problematic cases, application of one to three immunostains will usually suffice for classification. What is not clear is how accurately the histological type can be diagnosed on the basis of cytology or small biopsy specimens. Treatment of patients with advanced ovarian carcinoma with neoadjuvant therapy is becoming increasingly common. A large randomized clinical trial has shown that this approach offers comparable disease-specific survival rates with less morbidity, compared with the conventional approach of debulking surgery followed by chemotherapy.[33] We have developed a panel of nine immunomarkers that can be used to predict the ovarian carcinoma subtype.[34] The result for each of the immunostains is entered into an equation, which is used to predict the most likely histological type on the basis of the staining profile. The biomarker panel has been validated in two independent case series, although it has the drawback of requiring data for all nine markers; that is, it cannot impute missing data. Such a tool becoming useful for more than research purposes will depend on whether there is progress to full subtype-specific treatment, with treatment decisions based on cytology or small biopsy specimens.

Clinical Implications of Subtype Diagnosis

Some of the differences in subtype-specific management

in British Columbia include the following:

- All patients with high-grade serous carcinoma are referred for genetic counselling and *BRCA* testing.[35]
- Combination radiotherapy and chemotherapy is offered as adjuvant therapy for patients with mucinous, endometrioid, and clear cell carcinomas, whereas chemotherapy alone is offered to patients with high-grade serous carcinoma.[36,37]
- Patients with stage 1a mucinous or endometrioid carcinoma, without an undifferentiated component, are treated with surgery alone, whereas all patients with high-grade serous carcinoma, regardless of stage, are routinely treated with chemotherapy after surgery.[38]

A subset of mucinous carcinomas show high-level amplification of *HER-2*, and some patients have responded to trastuzumab therapy.[39] Promising subtype-specific targeted therapies that may enter clinical practice in the near future include *PARP* inhibitors for high-grade serous carcinoma and inhibitors of mutant *BRAF* for low-grade serous carcinoma,

A Tutorial for Ovarian Carcinoma Subtype Diagnosis

Images of two series of ovarian carcinomas are available on line at http://www.gpecimage.ubc.ca/aperio/images/transcanadian/.For the first set of cases – the training set – diagnoses are provided, whereas for the second test set, no diagnosis is given until the diagnosis is entered. This is an unselected series of cases and allows the observer to see how accurate his or her diagnosis is. These are the cases used as a training exercise for the trans-Canadian study on the reproducibility of ovarian carcinoma subtyping.[15]

References

1. Tavassoli FA, Deville P. World Health Organization classification of tumours. Pathology and genetics of tumours of the breast and female genital tract. Lyon, PA: IARC Press, 2003.
2. Gilks CB, Prat J. Ovarian carcinoma pathology and genetics: recent advances. Hum Pathol 2009;40:1213–23.
3. Fountain J, Trimble E, Birrer MJ. Summary and discussion of session recommendations. Gynecol Oncol 2006;103:S23–S25.
4. Köbel M, Kalloger SE, Huntsman DG, et al. Differences in tumor cell type in low versus high stage ovarian carcinomas. Int J Gynecol Pathol 2010;29;203–11.
5. Lund B, Thomsen HK, Olsen J. Reproducibility of histopathological evaluation in epithelial ovarian carcinoma. Clinical implications. APMIS 1991;99:353–8.
6. Cramer SF, Roth LM, Ulbright TM, et al. Evaluation of the reproducibility of the World Health Organization classification of common ovarian cancers. With emphasis on methodology. Arch Pathol Lab Med 1987;111:819–29.
7. Hernandez E, Bhagavan BS, Parmley TH, et al. Interobserver variability in the interpretation of epithelial ovarian cancer. Gynecol Oncol 1984;17:117–23.
8. Sakamoto A, Sasaki H, Furusato M, et al. Observer disagreement in histological classification of ovarian tumors in Japan. Gynecol Oncol 1994;54:54–8.
9. Stalsberg H, Abeler V, Blom GP, et al. Observer variation in histologic classification of malignant and borderline ovarian tumors. Hum Pathol 1988;19:1030–5.
10. Al-Hussaini M, Stockman A, Foster H, et al. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. Histopathology 2004;44:109–15.
11. Gilks CB, Ionescu DN, Kalloger SE, et al. Tumor cell type can be reproducibly diagnosed and is of independent prognostic significance in patients with maximally debulked ovarian carcinoma. Hum Pathol 2008;39:1239–51.
12. Han G, Gilks CB, Leung S, et al. Mixed ovarian epithelial carcinomas with clear cell and serous components are variants of high-grade serous carcinoma: an interobserver correlative and immunohistochemical study of 32 cases. Am J Surg Pathol 2008;32:955–64.
13. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol 2004;28:496–504.
14. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. Am J Surg Pathol 2007;31:1168–74.
15. Köbel M, Kalloger SE, Baker PM, et al. Diagnosis of ovarian carcinoma cell type is highly reproducible: a trans-Canadian study. Am J Surg Pathol 2010;34;984–93.
16. Malpica A. Grading of ovarian cancer: a histotype-specific approach. Int J Gynecol Pathol 2008;27;175–81.
17. Kommoss S, Schmidt D, Kommoss F, et al. Histological grading in a large series of advanced stage ovarian carcinomas by three widely used grading systems: consistent lack of prognostic significance. A translational research subprotocol of a prospective randomized phase III study (AGO-OVAR 3 protocol). Virchows Arch 2009;454:249–56.
18. Provenza C, Young RH, Prat J. Anaplastic carcinoma in mucinous ovarian tumors: a clinicopathologic study of 34 cases emphasizing the crucial impact of stage on prognosis, their histologic spectrum, and overlap with sarcomalike mural nodules. Am J Surg Pathol 2008;32:383–9.
19. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol 2006;25;52–8.
20. McCluggage WG. My approach to and thoughts on the typing of ovarian carcinomas. J Clin Pathol 2008;61:152–63.
21. Köbel M, Kalloger SE, Carrick J, et al. A limited panel of immunomarkers can reliably distinguish between clear cell and high-grade serous carcinoma of the ovary. Am J Surg Pathol 2009;33:14–21.
22. Sangoi AR, Soslow RA, Teng NN, et al. Ovarian clear cell carcinoma with papillary features: a potential mimic of serous tumor of low malignant potential. Am J Surg Pathol 2008;32;269–74.
23. Vang R, Shih IeM, Salani R, et al. Subdividing ovarian and peritoneal serous carcinoma into moderately differentiated and poorly differentiated does not have biologic validity based on molecular genetic and in vitro drug resistance data. Am J Surg Pathol 2008;32:1667–74.
24. Ayhan A, Kurman RJ, Yemelyanova A, Vang R, Logani S, Seidman JD, Shih IeM. Defining the cut point between low-grade and high-grade ovarian serous carcinomas: a clinicopathologic and molecular genetic analysis. Am J Surg Pathol 2009;33:1220–4.

25. Parker RL, Clement PB, Lesack DW, et al. Early recurrence of ovarian serous borderline tumor as high-grade carcinoma: a report of two cases. Int J Gynecol Pathol 2004;23;265–72.
26. O'Neil CJ, McBride HA, Connolly LE, et al. High-grade ovarian serous carcinoma exhibits significantly higher p16 expression than low-grade serous carcinoma and serous borderline tumour. Histopathology 2007;50:773–9.
27. O'Neil CJ, Deavers MT, Malpica A, Foster H, McCluggage WG. An immunohistochemical comparison between low-grade and high-grade ovarian serous carcinomas: significantly higher expression of p53, MIB1, BCL2, HER2/neu, and C-KIT in high-grade neoplasms. Am J Surg Pathol 2005;29:1034–41.
28. Kobel M, Reuss A, Bois A, et al. The biological and clinical value of p53 expression in pelvic high-grade serous carcinoma. J Pathol 2010;222:191–8.
29. Logani S, Oliva E, Amin MB, et al. Immunoprofile of ovarian tumors with putative transitional cell (urothelial) differentiation using novel urothelial markers: histogenetic and diagnostic implications. Am J Surg Pathol 2003;27:1434–41.
30. Soslow RA, Rouse RV, Hendrickson MR, et al. Transitional cell neoplasms of the ovary and urinary bladder: a comparative immunohistochemical analysis. Int J Gynecol Pathol 1996;15:257–65.
31. Cuatrecasas M, Catasus L, Palacios J, Prat J. Transitional cell tumors of the ovary: a comparative clinicopathological, immunohistochemical, and molecular genetic analysis of Brenner tumors and transitional cell carcinomas. Am J Surg Pathol 2009;33;556–67.
32. Kommoss F, Kommoss S, Schmidt D, et al. Survival benefit for patients with advanced-stage transitional cell carcinomas vs. other subtypes of ovarian carcinoma after chemotherapy with platinum and paclitaxel. Gynecol Oncol 2005;97;195–9.
33. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIc or IV ovarian cancer. N Engl J Med 2010;363:943–53.
34. Kalloger SE, Köbel M, Leung S, et al. Calculator for ovarian carcinoma subtype prediction. Mod Pathol 2011;24:512–21.
35. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
36. Nagai Y, Inamine M, Hirakawa M, et al. Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary. Gynecol Oncol 2007;107:469–73.
37. Swenerton KD, Santos JL, Gilks CB, et al. Histotype predicts the curative potential of radiotherapy: the example of ovarian cancers. Ann Oncol 2011;22:341–7.
38. Köbel M, Kalloger SE, Santos JL, et al. Tumor type and substage predict survival in stage I and II ovarian carcinoma: insights and implications. Gynecol Oncol 2009;116:50–6.
39. McAlpine JN, Wiegand KC, Vang R, et al. HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy. BMC Cancer 2009;9:433.