Review

Histologic Subtypes of Ovarian Carcinoma: An Overview

Robert A. Soslow, M.D.

Summary: Reproducible subclassification of ovarian carcinomas is biologically and increasingly therapeutically important. The traditional morphologic approach that ignores genotype and immunophenotype is subjective and therefore suboptimal. This review covers the prevalence, morphology, immunophenotype and, in some cases, genotype of each major ovarian cancer subtype. Serous carcinomas, frequently WT1 positive, are morphologically diverse and mimic other tumors. Most transitional cell carcinomas are closely related to them. Mucinous carcinomas are uncommon and should only be diagnosed after extraovarian primaries are excluded; true ovarian mucinous carcinomas are usually low stage. Intestinal and mullerian mucinous (seromucinous) tumors are histogenetically and clinically distinct. Ovarian endometrioid carcinomas almost always resemble endometrioid carcinomas of endometrium, express estrogen receptors (ER) but not WT1, and are frequently low grade and low stage. Ovarian clear cell carcinomas, negative for ER and WT1 and lacking p53 overexpression, have a limited morphologic repertoire and are frequently low stage at presentation. Clinical biology, immunohistochemistry, and genotype can be used to enhance diagnostic objectivity. Key Words: Ovarian carcinoma—Histologic subtype— Serous—Endometrioid—Mucinous—Clear cell.

The World Health Organization’s classification of ovarian tumors, taking advantage of traditional histomorphologic features, recognizes serous, mucinous, endometrioid, clear cell, transitional cell, and squamous ovarian neoplasms (1). Synthesizing the various features depends on empirically derived conventions, not objective criteria. As conventions change, so does our approach to subclassifying ovarian carcinomas—witness the vanishing primary mucinous carcinomas—witness the vanishing primary mucinous carcinomas and poorly differentiated endometrioid carcinomas and the difficulties regarding the separation of serous from transitional carcinomas and, in some cases, clear cell carcinomas. Although one could argue that tedious subclassification of ovarian carcinomas is probably not worth the trouble given the current therapeutic options (ie, most ovarian cancers are treated about the same way and have a terrible prognosis), I would make a point that reproducible subclassification of ovarian carcinomas is very important.

Emerging data support the idea that, instead of representing one disease with many faces, ovarian carcinoma constitutes at least several, and perhaps dozens, if not more, distinct disease entities. Examples include the narrow spectrum of ovarian carcinomas seen in BRCA1 and BRCA2 patients (2,3), the biologic distinctiveness of low- and high-grade serous carcinomas (4,5), molecular genetic pathways that link endometriosis with endometrioid and clear cell carcinomas (6–9), and etiologic relationships between serous borderline tumors and low-grade serous carcinoma (4,5), and between endometrioid borderline tumors and endometrioid carcinomas (10–13). Some of this is currently clinically relevant; it is increasingly recognized that low-grade serous (14), mucinous, and clear cell carcinomas (15–19) are intrinsically resistant to standard...
chemotherapeutic agents. Although specific therapies for each disease entity do not yet exist, standardizing diagnostic criteria will become essential as effective regimens are developed. Corollaries in other organ systems include the considerable data that link morphology, immunophenotype, and genotype in varieties of lymphoma, sarcoma, and renal neoplasia. The World Health Organization’s classification of lymphomas is a model candidate for an objective and reproducible system for diagnosis (1).

The criteria used for tumor grading and to separate borderline tumors from carcinomas depend on histologic subtype. For example, although it is commonly assumed that the presence of invasion separates borderline tumors from carcinomas, this is not always practiced in serous carcinoma, in which high-grade malignant cytologic features (even without stromal invasion) generally trigger a carcinoma diagnosis, and in clear cell carcinoma, in which papillary architecture (again without an obvious stromal response to invasion) in the right context defines carcinoma. So-called expansile invasion qualifies for carcinoma in the endometrioid and mucinous realms (10,11,20–23), although its equivalent in serous tumors, extensive micropapillary architecture (24,25), is not universally accepted as evidence of carcinoma (26–30). As for grading, none of the commonly used grading schemes is applicable to clear cell carcinomas (31–33), and the MD Anderson grading scheme pertains to serous carcinomas alone (21).

This review will cover the prevalence, morphology, immunophenotype, and, in some cases, genotype of each major ovarian cancer subtype. Differential diagnostic entities, particularly those that include other ovarian surface epithelial neoplasms, will be emphasized (Table 1). The differential diagnosis that concerns the distinction of surface epithelial carcinomas from other tumor types is presented in Table 2.

### SEROUS TUMORS

**Prevalence**

Based on modern criteria for histotyping ovarian carcinomas, approximately 80% to 85% of all ovarian carcinomas in Western, industrialized countries are serous (34). Perhaps as many as 95% of patients with

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**TABLE 1. Ovarian surface epithelial carcinoma characteristics**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Serous</td>
<td>Wide spectrum of morphologic features +WT1, p53*</td>
<td>+WT1, p53*</td>
</tr>
<tr>
<td>Intestinal mucinous</td>
<td>Fallopian tube intraepithelial carcinoma associated with high-grade carcinoma</td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>Glandular; at least focal intracytoplasmic mucin +ER, −WT1</td>
<td>−ER, −WT1</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Microcystic, papillary or adenofibromatous +ER, −WT1</td>
<td>−ER, −WT1</td>
</tr>
<tr>
<td>Transitional</td>
<td>Broad papillae, solid sheets +WT1, p53*</td>
<td>+WT1, p53*</td>
</tr>
</tbody>
</table>

*Overexpression.

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**TABLE 2. Ovarian surface epithelial tumors and mimickers**

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Surface epithelial tumor</th>
<th>Mimic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Serous</td>
<td>Yolk sac tumor</td>
</tr>
<tr>
<td></td>
<td>Endometrioid</td>
<td>Retiform Sertoli-Leydig cell tumor</td>
</tr>
<tr>
<td></td>
<td>Clear cell</td>
<td>Adult granulosa cell tumor with pseudopapillae</td>
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<tr>
<td></td>
<td>Transitional</td>
<td>Papillary thyroid carcinoma in struma ovarii</td>
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<tr>
<td></td>
<td></td>
<td>Mesothelioma</td>
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<tr>
<td></td>
<td></td>
<td>Ependymoma</td>
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<tr>
<td></td>
<td></td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Glandular</td>
<td>Serous</td>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td></td>
<td>Intestinal mucinous</td>
<td>Yolk sac tumor</td>
</tr>
<tr>
<td></td>
<td>Endometrioid</td>
<td>Sertoli and Sertoli-Leydig cell tumors</td>
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<tr>
<td></td>
<td>Clear cell</td>
<td>Adult granulosa cell tumor Wollfian tumor</td>
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<tr>
<td></td>
<td>Transitional</td>
<td>Ependymoma</td>
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<tr>
<td></td>
<td></td>
<td>Carcinoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma in teratoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Solid</td>
<td>Serous</td>
<td>Dysgerminoma</td>
</tr>
<tr>
<td></td>
<td>Endometrioid</td>
<td>Granulosa cell tumors</td>
</tr>
<tr>
<td></td>
<td>Clear cell</td>
<td>Carcinoma ex teratoma</td>
</tr>
<tr>
<td></td>
<td>Transitional</td>
<td>Metastatic neoplasms</td>
</tr>
</tbody>
</table>
International Federation of Gynecology and Obstetrics (FIGO) stages III-IV disease have serous carcinomas. FIGO stage I serous carcinomas are very uncommon. In the Memorial Sloan-Kettering Cancer Center study (12), only approximately one quarter of ovarian carcinomas confined to the pelvis (FIGO stages I and II) were FIGO stage I serous carcinomas, and only approximately one quarter of serous carcinomas confined to the pelvis were FIGO stage I. All low FIGO stage serous carcinomas in this study were high grade.

Morphology, Immunophenotype, and Genotype (Figs. 1–5)

Serous carcinomas show a very broad spectrum of histologic appearances, which contrasts with most other primary ovarian carcinomas in which morphologic variation is considerably less. The morphologic heterogeneity of serous carcinomas is likely an expression of the genetic and heterogeneity of these tumors and suggests that some tumors currently diagnosed as serous carcinomas represent transformation or progression from other tumor types. Most serous carcinomas demonstrate papillary and micropapillary architecture with evident slit-like spaces at least focally, but glandular, cribriform (24,25), solid, microcystic (35), and trabecular architecture can predominate. Cytologically, serous carcinomas typically contain columnar cells with pink cytoplasm, but examples with polygonal eosinophilic cells, clear cells, signet ring cells (35), and spindle cells certainly exist. Focal squamous differentiation (36) and elements resembling choriocarcinoma (37) can also be seen. It can be difficult to distinguish glandular or cribriform serous carcinomas...
from endometrioid carcinoma; solid or trabecular serous carcinomas from transitional carcinoma; microcystic serous carcinoma, particularly with signet ring cells, from mucinous carcinoma, including metastatic mucinous carcinoma; and serous carcinomas with clear cells from clear cell carcinoma. Other features that are characteristic of ovarian serous carcinoma and possibly useful in histologic subcategorization include the following: widespread WT1 expression (38–40), p53 overexpression and p53 mutation in high-grade varieties (41–44), association between BRCA1 or BRCA2 mutations and familial high-grade carcinomas (2,3,45), loss of BRCA1 expression in many high-grade carcinomas (46), coexistence of serous borderline tumor with low-grade carcinoma (4,5) and tubal intraepithelial carcinoma with high-grade carcinoma (47–50), and retention of BRAF or KRAS mutations in both serous borderline tumor and low-grade carcinoma (51–54). The criteria used for distinguishing serous borderline tumor and low-grade serous carcinoma have been reviewed in detail elsewhere (24–30,55,56).

Differential Diagnosis (Tables 1–3)
The approach to making a diagnosis of serous carcinoma involves recognizing a pattern that is consistent with the diagnosis and then excluding other possibilities, including metastases, such as those from an endometrioid serous carcinoma. It is also occasionally necessary to use ancillary information or diagnostic techniques to support one’s impression. Recommended strategies include assays for WT1 and p53 expression and a search for a precursor lesion, such as serous borderline tumor (for low-grade serous carcinoma) and intraepithelial carcinoma, particularly of the fallopian tube (for high-grade serous carcinoma). For example, features favoring serous carcinoma with cribriform architecture over endometrioid carcinoma include WT1 expression and the presence of micropapillae and slit-like spaces. Features in favor of endometrioid carcinoma with cribriform architecture include the presence of endometriosis, an endometrioid adenofibromatous tumor (including endometrioid borderline tumor), and squamous metaplasia. Another problem concerns the coexistence of serous carcinomas in endometrium and ovary and occult serous endometrial cancers that present like ovarian carcinoma. Unlike ovarian, peritoneal and fallopian tubal serous carcinomas, endometrial serous carcinomas frequently lack WT1 expression (38,39,57). When WT1 is used to adjudicate whether serous carcinomas in endometrium and ovary are synchronous, a WT1 immunostain generally supports that they are not (57). Most cases fail to demonstrate WT1 immunoreactivity, supporting the idea that these are metastatic endometrial serous carcinomas (57), even when the volume of disease predominates in ovary and peritoneum. A discussion of other entities in the differential diagnosis follows later in the text.

INTESTINAL MUCINOUS TUMORS
Prevalence
Primary ovarian mucinous carcinomas (POMCs) are very uncommon; a recent publication indicated that less than 3% of all ovarian carcinomas are mucinous (34,58). Approximately one half to two thirds are FIGO stage I in industrialized, Western countries (20). Although they are rare, POMCs make it to a top 3 position in the distribution of FIGO stage I tumors (12).

Morphology, Immunophenotype, and Genotype (Fig. 6)
POMCs display a limited range of histologic appearances. Although identifying intracytoplasmic mucin is mandatory, many mucinous tumors lack obvious apical mucin in large parts of tumor, thereby imparting an endometrioid appearance. Mucinous borderline tumors lacking goblet cells are classified separately from

TABLE 3. Serous features

- Broad range of histologic features
- At least focal slit-like spaces, irregular luminal contours
- Frequent WT1 expression*
- Low-grade: serous borderline tumor associated, BRAF/K-ras mutation, ER/PR expression
- High-grade: tubal intraepithelial carcinoma associated, p53 mutation, p16 expression, loss of BRCA1 expression
- BRCA1 or BRCA2 family
- Other entities are excluded

*Search for an endometrial primary if a serous carcinoma fails to express WT1.
intestinal mucinous neoplasms; they have been referred to as Mullerian mucinous or endocervical mucinous or seromucinous or mixed epithelial neoplasms with a mucinous component. They are mentioned briefly during the discussion of endometrioid borderline tumors and clear cell carcinomas and will be discussed in more detail along with the mixed epithelial neoplasms. Most primary mucinous carcinomas display transitions from intestinal mucinous borderline to carcinoma. Architecturally, the distinction with borderline tumor is often based on the presence of so-called expansile invasion and, less commonly, on the presence of tumor nests that haphazardly infiltrate stroma. Details about distinguishing intestinal mucinous borderline tumors from carcinomas have been reviewed previously (21–23).

POMCs preferentially express CK7 over CK20 (59–62). Compared to colorectal carcinomas, they are negative for racemase and nuclear β-catenin (63). They are p16 negative, in contrast to endocervical adenocarcinomas (64), and lack expression of estrogen receptors (ERs) (65), unlike endometrioid carcinomas. Compared to many pancreatic ductal carcinomas, about half of which lack SMAD4/DPC4 expression, SMAD4 expression is retained (60), but POMCs lack mesothelin and fascin (66). Finally, K-ras mutations are common in ovarian mucinous carcinomas (67,68).

<table>
<thead>
<tr>
<th>TABLE 4, Intestinal mucinous features</th>
</tr>
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<tbody>
<tr>
<td>• Intracytoplasmic mucin, expansile invasion</td>
</tr>
<tr>
<td>• Intestinal mucinous borderline tumor associated</td>
</tr>
<tr>
<td>• CK7 &gt; 20, retained SMAD4 expression</td>
</tr>
<tr>
<td>• Negative expression of racemase, nuclear β-catenin, ER, p16, mesothelin, fascin</td>
</tr>
<tr>
<td>• K-ras mutation</td>
</tr>
<tr>
<td>• Other entities are excluded: exclude metastasis</td>
</tr>
</tbody>
</table>

Differential Diagnosis (Tables 1–6)

The main differential diagnostic considerations here involve endometrioid carcinoma, low-grade serous carcinoma with intraluminal mucin (Fig. 2), high-grade serous carcinoma with microcysts and signet ring cells, and metastatic adenocarcinoma, including examples from the upper gastrointestinal and pancreatobiliary tracts, colon, and appendix. Coexisting mucinous borderline tumor and the absence of endometriosis, an endometrioid adenofibromatous tumor, and squamous metaplasia favor a mucinous neoplasm instead of an endometrioid tumor. WT1 expression is typical of serous carcinoma. Predominance of CK7 expression over CK20 (59–62), retained DPC4 expression (60), and absence of bilaterality, tumor nodularity, ovarian surface involvement, destructive stromal invasion, and lymphovascular invasion all favor POMC over metastatic mucinous carcinoma (69,70). Unusual problems include the differentiation of metastatic endocervical carcinoma (66,71) and pulmonary carcinomas from primary mucinous ovarian carcinomas (72). p16 expression is typical of endocervical carcinomas of the usual type (66,69), and TTF-1 expression is frequently encountered in pulmonary adenocarcinomas metastatic to ovaries (70).

ENDOMETRIOID TUMORS

Prevalence

With the recognition that many serous carcinomas were previously diagnosed as endometrioid carcinomas, the overall perceived prevalence of this tumor type has decreased. Nevertheless, it is probably still the second most common ovarian carcinoma subtype in the West, accounting for approximately 10% of all ovarian carcinomas (34). It is the most common tumor represented by FIGO stage I carcinomas, probably constituting at least 50% of such cases (12). Most endometrioid carcinomas are FIGO stage I or II.

<table>
<thead>
<tr>
<th>TABLE 5. Mucinous tumors: features favoring metastasis (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilateral disease</td>
</tr>
<tr>
<td>• Surface involvement</td>
</tr>
<tr>
<td>• Destructive stromal invasion</td>
</tr>
<tr>
<td>• Nodular growth pattern</td>
</tr>
<tr>
<td>• Single cells/signet ring cells</td>
</tr>
<tr>
<td>• Vascular invasion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 6. Mucinous tumors: algorithm for distinguishing primary and metastatic mucinous carcinoma (58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral mucinous carcinomas: metastatic</td>
</tr>
<tr>
<td>Unilateral mucinous carcinomas &lt;10 cm: metastatic</td>
</tr>
<tr>
<td>Unilateral mucinous carcinomas &gt;10 cm: primary ovarian</td>
</tr>
</tbody>
</table>

FIG. 6. Well-differentiated ovarian mucinous carcinoma showing a labyrinthine pattern, evidence of expansile invasion.
Morphology, Immunophenotype, and Genotype (Figs. 7–10)

Endometrioid ovarian tumors resemble their endometrial counterparts. Architectural patterns containing tubules, cribriform structures, solid, sheetlike growth, and papillae should be present in the context of an easily recognized endometrial-like background. Most endometrioid carcinomas are associated with endometriosis, endometrioid borderline tumor, or a synchronous endometrial neoplasm of endometrioid type (10,11,13). In general, the cytologic features are concordant with the architectural features such that markedly atypical and highly proliferative cells are not arranged in simple tubules or papillae. Most endometrioid carcinomas contain either squamous or mucinous differentiation and may show secretory features. Occasional examples demonstrate sex cord-like features (73,74) or spindle cells (75). Other features that are characteristic of endometrioid carcinomas include nuclear expression of ER, progesterone receptor (PR), and β-catenin (76–79). In contrast to the usual serous carcinoma, endometrioid carcinomas lack WT1 expression (80,81) and p53 overexpression, although this has been described in purported poorly differentiated varieties (82). Results from a gene expression analysis (83) support the idea that ovarian cancers diagnosed as high-grade or poorly differentiated endometrioid carcinomas are not biologically related to low-grade endometrioid carcinomas. They demonstrate a high degree of similarity to high-grade serous carcinomas instead.

Mutations in CTNNB-1 (β-catenin) (76–78,84), PI3CA (encoding phosphotidylinositol 3-kinase [PI3K]) (83,85), and PTEN (6,77) have been reported to have high levels of microsatellite instability (76,77).

FIG. 7. Typical endometrioid carcinoma, resembling endometrioid carcinoma of the endometrium.

FIG. 8. Endometrioid carcinoma with a papillary pattern, recalling a serous neoplasm.

FIG. 9. Endometrioid carcinoma with spindle cells, a mimic of carcinosarcoma.

FIG. 10. Endometrioid carcinoma with secretory-like change. This should not be confused with clear cell carcinoma.
Endometrioid Borderline Tumor

Endometrioid carcinoma should only be diagnosed when there is convincing evidence of invasion. The pattern least subject to differences in interpretation is destructive stromal invasion, especially when it is found at the periphery of rounded, lobulated tumor nests. Destructive stromal invasion is diagnosed when there are irregularly shaped groups of epithelial cells, glands, or nests within stroma displaying an edematous or desmoplastic reaction. This pattern resembles the typical pattern of endometrioid carcinoma when it invades myometrium. A more common pattern, generally assumed to represent invasion, is the so-called expansile pattern (10,11; Fig. 6). Although neither a stromal reaction nor jagged infiltration is seen, this pattern is thought to represent invasion because confluent growth of epithelium excludes stroma, thereby implying invasion thereof. Criteria for distinguishing borderline tumor from carcinoma with expansile invasion are the same as those that permit distinction of complex atypical hyperplasia from endometrioid carcinoma of the endometrium (86,87); extensive gland fusion, large gland cribriforming, maze-like lumens, and extensive papillary architecture are considered evidence of invasion (10,11,13). Despite the fact that both expansile and destructive types of invasion are usually given equal billing, carcinomas with destructive invasion are likely to be more aggressive than those without. There is not a single well-documented example of an endometrioid carcinoma, grade 1 or 2 (of 3) and FIGO stage IA or IB, showing only expansile invasion, that has metastasized (13). However, I do not know of a study that describes the histologic details of ovarian primaries in the setting of high FIGO stage endometrioid ovarian carcinoma.

Although the use of the terms “borderline” and “low malignant potential” in reference to endometrioid tumors is historically rather well entrenched and even morphologically accurate, the clinical outcomes are benign (10,11). This distinguishes the endometrioid borderline tumors (as well as the intestinal mucinous, clear cell, and Brenner varieties) from the serous and seromucinous borderline tumors that display both architectural atypia and a clinical profile that includes frequent presentation at high stage and recurrences and occasional deaths. I would therefore favor separating the serous and seromucinous borderline tumors from the endometrioid, intestinal mucinous, clear cell, and Brenner tumors previously considered borderline; the “atypical proliferative” nomenclature popularized by Russell and colleagues seems appropriate for the latter tumors.

Differential Diagnosis (Tables 1, 2, and 7; Fig. 11)

The differential diagnosis of ovarian endometrioid carcinoma includes high-grade serous carcinoma when the cytologic features are highly atypical (Fig. 11), low-grade serous carcinoma in examples with cytologically bland cribriform architecture (Figs. 2 and 3), mucinous

### TABLE 7. Endometrioid features

- Endometrioid-like, metaplasias, secretory change, expansile invasion
- Endometriosis, endometrioid borderline tumor, endometrioid uterine carcinoma associated
- ER/PR and nuclear β-catenin expression; not WT1
- CTNNB1 (β-catenin), PTEN mutation and PI3K mutation, microsatellite instability-high (MSI-H)
- Other entities are excluded

### TABLE 8. Clear cell features

- Papillary, tubulocystic, solid, hobnail, frequently clear cytoplasm
- Endometriosis, clear cell borderline tumor associated
- Low ER/PR, WT1, p53, mib-1 expression
- MSI-H, PTEN mutation
- Lack of features that define other entities
  - Metaplasias, secretory changes
  - Multilayering, serrated luminal profiles

### TABLE 9. Papillary tumors containing clear cells:

<table>
<thead>
<tr>
<th>Clear cell carcinoma (CCC)</th>
<th>Serous carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral, low stage</td>
<td>Bilateral, high stage</td>
</tr>
<tr>
<td>Round papillae</td>
<td>Elongate, hierarchical branching</td>
</tr>
<tr>
<td>Hyaline, edematous stroma</td>
<td>Fibrous stroma</td>
</tr>
<tr>
<td>Hobnail cells, cuboidal</td>
<td>Columnar cells</td>
</tr>
<tr>
<td>Monolayer</td>
<td>Cellular tufting, micropapillae</td>
</tr>
<tr>
<td>Uniform nuclei</td>
<td>Pleomorphic nuclei</td>
</tr>
<tr>
<td>Decreased mitotic activity*</td>
<td>High mitotic rate</td>
</tr>
<tr>
<td>Other CCC patterns</td>
<td>Slit-like spaces</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>No endometriosis</td>
</tr>
<tr>
<td>WT1/−/ER−/p53−</td>
<td>WT1+/ER variable/p53+</td>
</tr>
</tbody>
</table>

* indicates approximately 5 mitotic figures/10 high-power fields.
carcinoma (both primary and metastatic) when there is inapparent intracytoplasmic mucin, clear cell carcinoma when there are numerous clear cells (Fig. 10), and transitional carcinoma when there is extensive solid growth (Fig. 4). These distinctions can usually be made by giving attention to the presence of a precursor lesion such as endometriosis or endometrioid borderline tumor, the resemblance to eutopic endometrioid proliferations, the presence of metaplasias common to endometrioid tumors, and the demonstration of ER and PR expression without WT1 expression or overexpression of p53. For example, a cytologically bland, cribriform tumor unassociated with endometriosis and showing WT1 expression along with ER and PR expression would likely be a low-grade serous carcinoma. An endometriosis-associated tumor composed of moderately atypical clear cells lining simple, back-to-back tubules and retaining ER/PR expression would likely be an endometrioid carcinoma, not a clear cell carcinoma (see the following). A carcinoma that expressed CK20 and CDX2 without CK7 or ER would support enteric differentiation, and diffuse p16 expression would suggest the possibility of a metastatic endocervical carcinoma.

**CLEAR CELL TUMORS**

**Prevalence**

Although rare, clear cell carcinoma is the third most common ovarian carcinoma in North America, where it accounts for approximately 5% of all ovarian tumors (34). Like endometrioid carcinomas, it is disproportionately represented in FIGO stages I and II. It constitutes a larger percentage of ovarian cancer in Japanese women, however (15). Between 20% (12) and 50% (88) of low-stage ovarian carcinomas are clear cell carcinomas, and
 unlike serous carcinomas, less than one half of clear cell carcinomas are disseminated at presentation (88–90).

Morphology, Immunophenotype, and Genotype (Tables 8 and 9; Figs. 12–15)

Clear cell carcinomas display a rather limited architectural inventory; only papillary, tubulocystic, and solid architectural varieties are recognized. The typical clear cell carcinoma is composed of hobnail cells with clear cytoplasm. The “oxyphilic variant,” characterized by eosinophilic tumor cells growing in classical clear cell carcinoma architectural patterns, has also been described. The nuclei of clear cell carcinomas, although large, atypical, and frequently featuring a large nucleolus, do not often show striking pleomorphism. The papillae of clear cell carcinomas differ from those of serous and endometrioid carcinomas—tumors that may display similar morphologic features. Clear cell carcinoma papillae are short and round and may show eosinophilic and hyalinized stroma. There are generally only 1 or 2 layers of cells lining the papillae, which contrast with the prominent tufting usually seen in serous carcinomas (Table 9). At least half of clear cell carcinomas are associated with endometriosis, particularly atypical endometriosis, or endometriosis-associated tumors, such as endometrioid and seromucinous borderline tumors, and many contain a tubulocystic adenofibromatous component with a range of cytologic atypia. Some clear cell carcinomas are predominantly or entirely adenofibromatous, and many of these show only focally marked cytologic atypia. A recent publication (91) supports the idea that clear cell adenocarcinomas associated with clear cell adenofibromatous components are a subgroup of ovarian clear cell adenocarcinomas, with distinct clinicopathologic characteristics.

Recent work indicates that clear cell carcinomas can be reproducibly diagnosed when the cytologic and architectural features in a given tumor are classic and homogeneous (92). In contrast, tumors containing clear cells with heterogeneous features (Fig. 5), (many of which had been diagnosed as mixed and serous clear cell carcinomas) carcinomas were not reproducibly diagnosed. Using rigorous application of diagnostic criteria and immunohistochemical staining, nearly all heterogeneous tumors would be better considered serous carcinomas with cells showing cytoplasmic clearing. In general, then, tumors containing clear cells, but lacking typical clear cell carcinoma architecture, are likely not examples of clear cell carcinoma. This point was emphasized in another recent publication (93).

The immunophenotype of clear cell carcinoma has not been extensively studied, both because the tumor is rather uncommon and also because it has historically been difficult to separate this tumor with confidence from endometrioid and serous carcinomas. In general, clear cell carcinomas tend to lack ER and WT1 expression (92,94–96). p53 expression can be encountered, but diffuse and strong overexpression of the sort seen in most high-grade serous carcinomas is not characteristic (97–99). Positive markers of clear cell differentiation have not been extensively tested. Recently reported examples include hypoxia-inducible factor 1 alpha (100), human kidney injury molecule-1 (101), hepatocyte nuclear factor-1 beta (8,102,103), and glypican-3 (104). Until such markers are studied in more detail, we will have to rely on the absence of ER and WT1 expression for diagnostic help.

Mutations in K-ras (105,106) and PTEN (6) have been reported, as well as several examples of microsatellite instability-high clear cell carcinoma (107–109).

Clear Cell Borderline Tumor (Fig. 14)

Clear cell borderline tumors have been reported in the literature (110,111), but this remains a vanishingly rare diagnosis. Tumors that have been diagnosed as clear cell borderline tumors are adenofibromatous, containing small tubules lined by flattened or cuboidal cytologically atypical clear cells. They are distinguished from clear cell carcinomas with a tubulocystic pattern by evidence of stromal invasion that exceeds microinvasion. In this context, a borderline tumor would retain densely collagenized or fibromatous stroma, whereas a carcinoma would demonstrate stromal edema, myxomatous change, or desmoplasia. The tubules of a borderline tumor should be regularly distributed, and those of a carcinoma are usually described as haphazardly arranged. Extensive sampling of tumors that resemble clear cell borderline tumor is recommended before establishing this diagnosis.

As mentioned previously, clear cell carcinomas, particularly papillary tumors, can be diagnosed without evident stromal invasion, which means that papillary clear cell borderline tumors cannot be diagnosed, at least using
historical criteria. Because occasional papillary clear cell carcinomas have been misdiagnosed as serous borderline tumors (112) and some seromucinous borderline tumors contain foci of bona fide papillary clear cell carcinomas (unpublished data), particular attention should be paid to the cytologic appearance of clear cells in papillary tumors. I would make a diagnosis of clear cell carcinoma in these settings if there was at least focal cytologic atypia of the variety seen in clear cell carcinoma, and the immunohistochemical results supported that diagnosis. It is currently debatable whether clear cell carcinoma should be diagnosed in the presence of an absolutely typical clear cell carcinoma architecture when the cells are clear and hobnail but not at all cytologically atypical (Table 10) (112).

**Differential Diagnosis (Tables 1, 2, and 8–10; Figs. 5 and 10)**

The differential diagnosis of clear cell carcinoma in the context of other surface epithelial tumors includes serous carcinoma (Fig. 5), serous borderline tumor (Fig. 15), and endometrioid carcinoma (Fig. 10). When confronted with a papillary ovarian carcinoma showing high nuclear grade, the choices are essentially restricted to serous and clear cell carcinomas (in the surface epithelial category). Rounded papillary cores with hyaline, surrounded by 1 or 2 layers of hobnail cells with uniform, but highly atypical nuclei, favor clear cell carcinoma (Fig. 12). A clear cell tumor demonstrating serous carcinoma features should not be diagnosed as clear cell carcinoma. WT1 expression, especially along with ER expression, would strongly favor a serous neoplasm over clear cell carcinoma. Occasional papillary clear cell carcinomas exhibiting all of the characteristic architectural features of clear cell carcinomas, but lacking diffusely atypical cells, may resemble serous borderline tumors (Fig. 15). Clues to the correct diagnosis here include an adenofibromatous gross appearance, finding an associated endometriotic cyst, and identifying even occasional hobnail cells with nuclear atypia. Clinical features should also be contributory because bilateral clear cell carcinomas and those that are disseminated at presentation are much less commonly encountered compared to serous neoplasms (92,112). The immunophenotypic guidelines discussed above would also apply to this differential diagnosis. Endometrioid carcinomas may mimic clear cell carcinomas when they are papillary and display secretory features (Fig. 10) and when tumor cell cytoplasm is squamoid and contains abundant glycogen (93). The traditional approach to this problem was to restrict a diagnosis of clear cell carcinoma in this setting to tumors with unequivocally high nuclear grade, and this is still absolutely relevant. We would still hesitate to place a cytologically high-grade clear cell tumor in the clear cell carcinoma category, particularly if mixed with a clear-cut endometrioid component, unless it also demonstrated characteristic architectural features of clear cell carcinoma.

**TRANSITIONAL CELL TUMORS**

**Prevalence**

The true prevalence of transitional carcinoma is impossible to ascertain because it is not diagnosed reproducibly. Transitional carcinomas that are morphologically and immunophenotypically distinct from serous carcinomas are very uncommon, however. Carcinomas with a transitional cell pattern that arise in Brenner tumors (so-called malignant Brenner tumors) are also exceedingly rare.

**Morphology and Immunophenotype**

 Transitional carcinomas should resemble urothelial carcinomas. When they are composed of cytologically low-grade cells with longitudinal nuclear grooves and arranged in broad papillae, they can be recognized easily; these cases are extraordinary, however. Cytologically high-grade tumors forming broad papillae frequently also contain microcysts, slit-like fenestrations and small, filiform papillae, making distinction from serous carcinoma almost impossible (Fig. 4). Squamous differentiation and psammoma bodies can also be seen. These tumors express WT1 (113) and frequently overexpress p53, which is identical to high-grade ovarian serous carcinoma (114) and different from urothelial carcinoma.

**Differential Diagnosis**

The differential diagnosis of transitional carcinoma of ovary primarily includes serous carcinoma and endometrioid carcinoma when metastasis from the urinary tract has been excluded. Although it may be impossible to separate high-grade serous and transitional cell carcinomas confidently, it is perhaps worthwhile to distinguish between them when the architectural and cytologic features are homogeneous and no serous features are appreciated; this distinction may benefit patients with transitional cell carcinomas, who have shown, in several reports, superior responses to chemotherapy (115–117). Patterns of omental dissemination might also differ in serous and transitional carcinomas, which theoretically could account for the reported clinico-pathologic disparities (115,118). A high-grade tumor forming broad papillae and solid sheets without slit-like spaces or ragged luminal contours could be placed in the transitional cell category (119), but if these latter features were present even focally, I would place the tumor in the serous group. Because both endometrioid and transitional cell
carcinomas can show papillae, solid sheets and squamous differentiation, they can be confused with one another. I would place such a tumor in the endometrioid category if endometrioid tubules were found, there was associated endometriosis, or an endometrioid adenofibromatous tumor and tumor cells expressed ER without WT1. I would favor a transitional carcinoma if WT1 expression was evident and endometrioid features other than squamous differentiation were lacking.

MIXED EPITHELIAL OVARIAN TUMORS

Currently, mixed epithelial ovarian tumors (MOTs) (i.e. mixed endometrioid and serous carcinomas) can be diagnosed when at least 2 histologically distinctive elements are present and each constitutes at least 10% of the tumor. I would emphasize here that, in my opinion, the elements should be obvious, separable, and characteristic to diagnose a MOT; and the immunophenotype of each component should be distinctive as well. MOTs should not be diagnosed when the overall morphology is a hybrid of features generally encountered in different ovarian cancer subtypes. For example, a cribriform tumor composed of pleomorphic cells with ragged luminal contours and lacking confirmary endometrioid features should not be considered a mixed endometrioid and serous carcinoma. My own practice is to diagnose these as high-grade serous carcinomas, but immunohistochemistry can be used to adjudicate difficult or controversial cases. These tumors are generally diffusely WT1 positive, as expected in serous carcinoma. Another important example, discussed in preceding paragraphs, is the occasional tendency of serous carcinomas to demonstrate clear cell features; these tumors as well are almost never examples of mixed serous and clear cell carcinomas. They are instead pure, high-grade serous carcinomas, with diffuse WT1 expression. Given these examples, the incidence of bona fide MOTs is probably lower than what is currently reported.

One well-documented type of MOT is the seromucinous borderline tumor (120–123), which belongs to a spectrum of neoplasms, ranging from pure endocervical or Mullerian mucinous borderline tumors to mixed endometrioid and mucinous borderline tumors and carcinomas. Seromucinous borderline tumors characteristically demonstrate the low-power appearance of serous borderline tumors, with intracystic hierarchical papillary branching and, unlike serous borderline tumor, an association with endometriosis. The lesional cells here are a mixture of endocervical-type cells with apical mucin (but not goblet cells), ciliated cells, and so-called indifferent cells. As a group, their clinical behavior is very similar to that of serous borderline tumors, but different from intestinal mucinous, endometrioid, Brenner, and clear cell border-line tumors, all of which are benign.

UNDIFFERENTIATED CARCINOMAS

Undifferentiated carcinoma should be regarded a diagnosis of exclusion. Currently, the absence of histological differentiating features is considered sufficient to make this diagnosis. I would argue that it is necessary to exclude metastatic carcinomas and nonepithelial neoplasms as well. Undifferentiated carcinomas are probably a very heterogeneous group. One specific type of undifferentiated carcinoma, albeit of endometrium, has been described by the MD Anderson group (124). The tumors are formed of sheets of small cells without glands. Immunohistochemical evidence of epithelial differentiation in these tumors may be hard to elicit. In general, it has not yet been defined whether immunohistochemistry should be used to distinguish between undifferentiated ovarian carcinoma and other surface epithelial tumors. Despite that, I currently classify carcinomas composed of solid sheets as serous if they are diffusely WT1 positive and other mimics have been excluded.

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