Review

Histologic Subtypes of Ovarian Carcinoma: An Overview

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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 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

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TABLE 1. *Ovarian surface epithelial carcinoma characteristics*

Serous	Wide spectrum of morphologic features Fallopian tube intraepithelial carcinoma associated with high-grade carcinoma Serous borderline tumor associated with low-grade carcinoma	+WT1, p53*
Intestinal mucinous	Glandular; at least focal intracytoplasmic mucin Intestinal mucinous borderline tumor also present	−ER, −WT1

Endometrioid	Glandular or papillary; "endometrial" appearance;
	  Squamous differentiation, endometriosis, endometrioid
	  adenofibroma or endometrial cancer also present
		+ER, −WT1

Clear cell	Microcystic, papillary or adenofibromatous Endometriosis or clear cell borderline tumor also present	−ER, −WT1
Transitional cell	Broad papillae, solid sheets	+WT1, p53*

*Overexpression.

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

TABLE 2. *Ovarian surface epithelial tumors and mimickers*

| Morphology	Surface epithelial tumor	Mimic
Papillary	Serous	Yolk sac tumor
	Endometrioid	Retiform Sertoli-Leydig cell tumor
	Clear cell	Adult granulosa cell tumor with pseudopapillae
	Transitional	Papillary thyroid carcinoma in struma ovarii
		Mesothelioma
		Ependymoma
		Metastatic carcinoma
Glandular	Serous	Embryonal carcinoma
	Intestinal mucinous	Yolk sac tumor
	Endometrioid	Sertoli and Sertoli-Leydig cell tumors
	Clear cell	Adult granulosa cell tumor
		Wolffian tumor
		Ependymoma
		Carcinoid
		Carcinoma in teratoma
		Metastatic carcinoma
Solid	Serous	Dysgerminoma
	Endometrioid	Granulosa cell tumors
	Clear cell	Carcinoma ex teratoma
	Transitional	Metastatic neoplasms
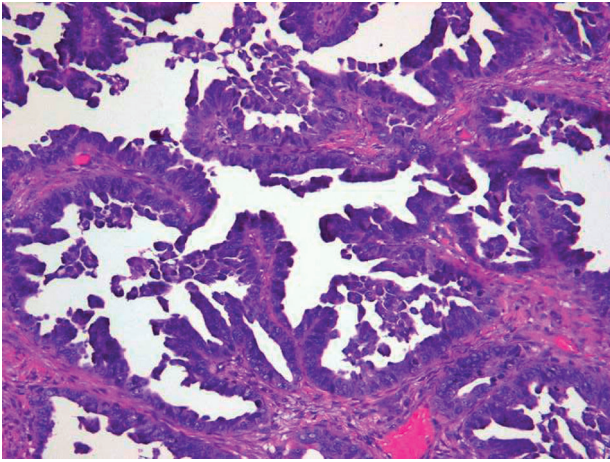
FIG. 1. Typical high-grade serous carcinoma with a papillary pattern and high nuclear grade.
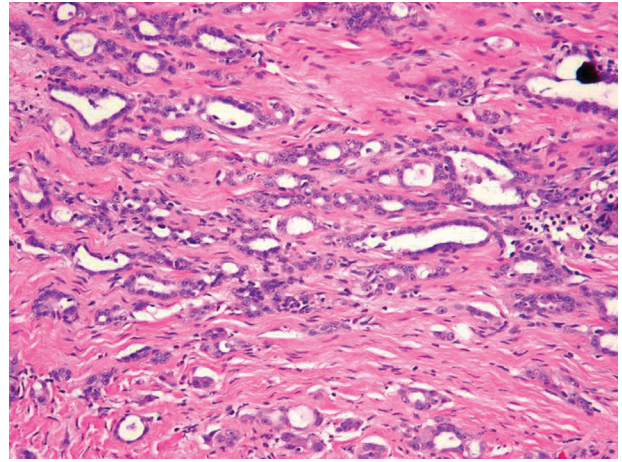

FIG. 3. Low-grade serous carcinoma with a glandular pattern.

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
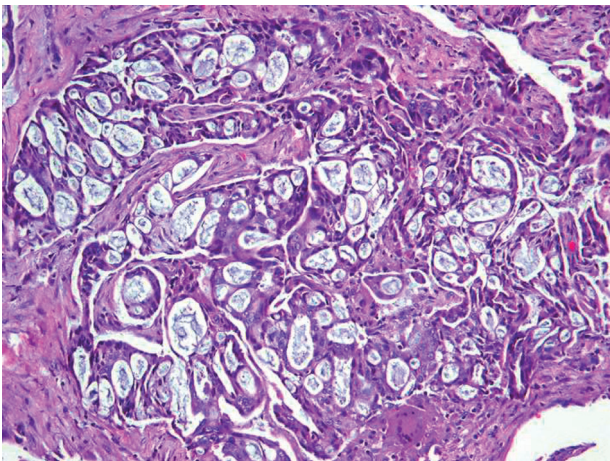

FIG. 2. Low-grade serous carcinoma with a cribriform and microcystic pattern, resembling endometrioid and mucinous carcinoma.
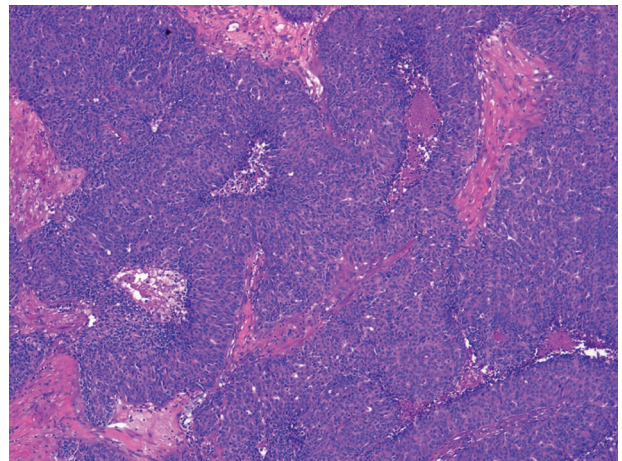

FIG. 4. High-grade serous carcinoma growing in sheets and broad papillae, mimicking transitional cell carcinoma.
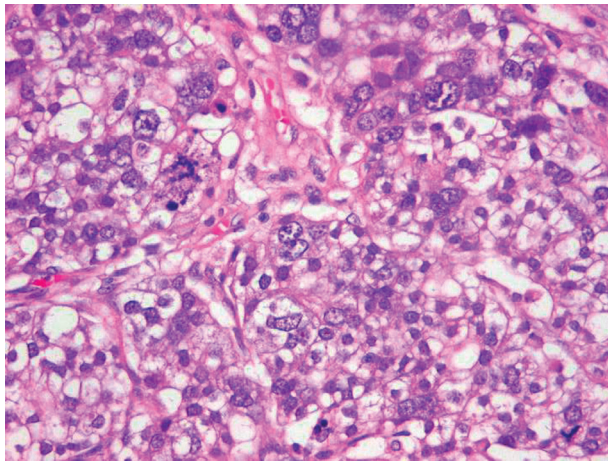
FIG. 5. High-grade serous carcinoma containing clear cells; tumors such as these have been mistaken for clear cell carcinomas with a solid pattern.

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 endometrial 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.
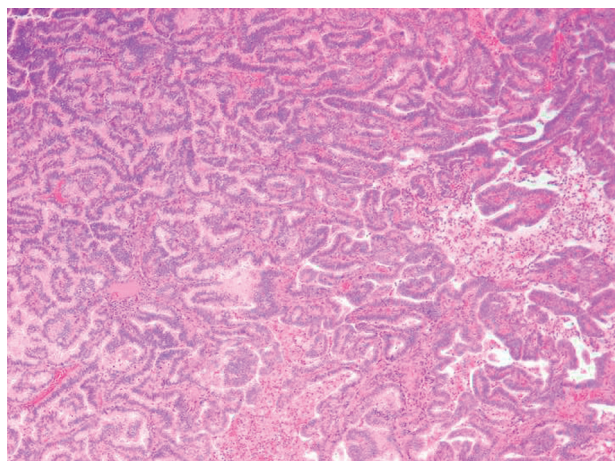
FIG. 6. Well-differentiated ovarian mucinous carcinoma showing a labyrinthine pattern, evidence of expansile invasion.

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 4. *Intestinal mucinous features*

- Intracytoplasmic mucin, expansile invasion
- Intestinal mucinous borderline tumor associated
- CK7 > 20, retained SMAD4 expression
- Negative expression of racemase, nuclear β-catenin, ER, p16, mesothelin, fascin
- *K-ras* mutation
- Other entities are excluded: exclude metastasis

TABLE 5. *Mucinous tumors: features favoring metastasis (72)*

- Bilateral disease
- Surface involvement
- Destructive stromal invasion
- Nodular growth pattern
- Single cells/signet ring cells
- Vascular invasion

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 6. *Mucinous tumors: algorithm for distinguishing primary and metastatic mucinous carcinoma (58)*

Bilateral mucinous carcinomas: metastatic
Unilateral mucinous carcinomas <10 cm: metastatic
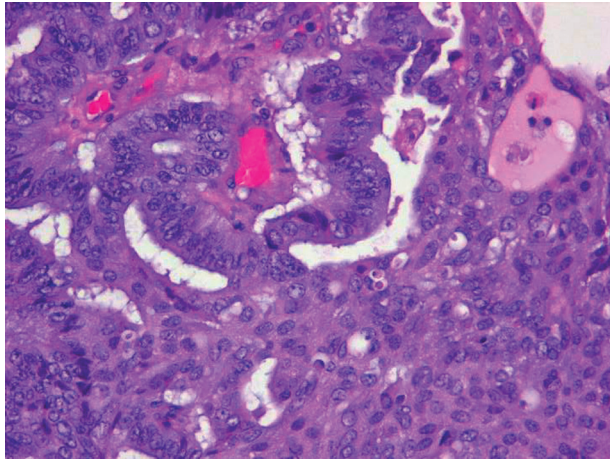Unilateral mucinous carcinomas >10 cm: primary ovarian

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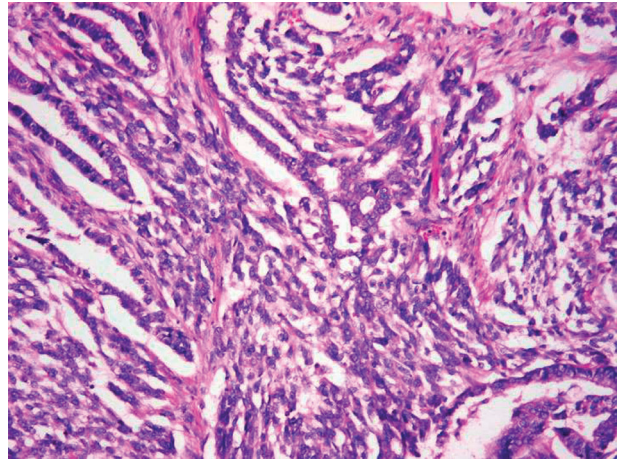

FIG. 9. Endometrioid carcinoma with spindle cells, a mimic of carcinosarcoma.

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).
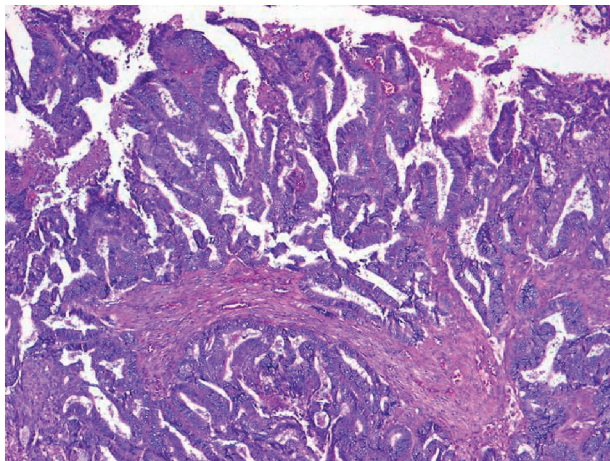

FIG. 8. Endometrioid carcinoma with a papillary pattern, recalling a serous neoplasm.
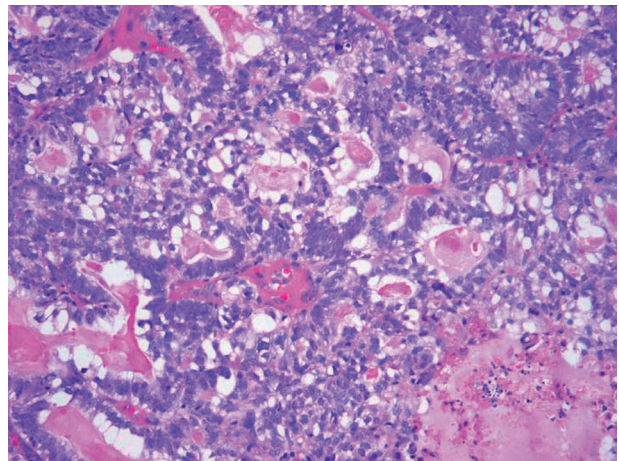

FIG. 10. Endometrioid carcinoma with secretory-like change. This should not be confused with clear cell carcinoma.
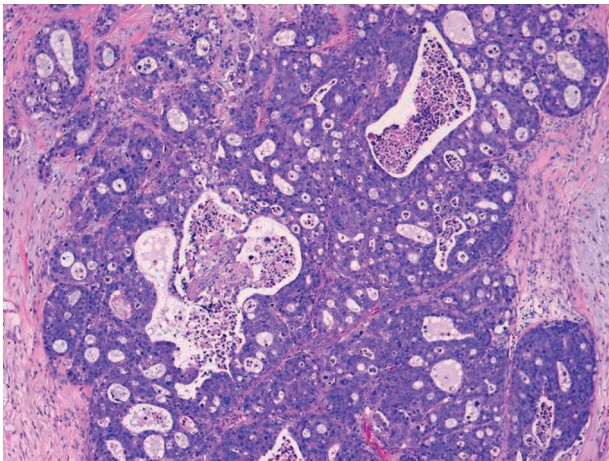
FIG. 11. High-grade serous carcinoma with a cribriform pattern resembling endometrioid carcinoma.

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

TABLE 7. *Endometrioid features*

- Endometrial-like, metaplasias, secretory change, expansile invasion
- Endometriosis, endometrioid borderline tumor, endometrioid uterine carcinoma associated
- ER/PR and nuclear β-catenin expression; not WT1
- *CTNNB-1* (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

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 9. *Papillary tumors containing clear cells: high nuclear grade*

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

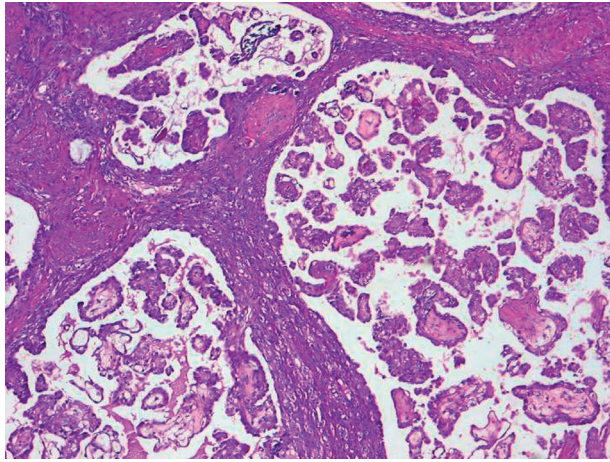* indicates approximately 5 mitotic figures/10 high-power fields.

FIG. 12. Clear cell carcinoma: papillary pattern.

FIG. 14. Clear cell carcinoma, solid pattern, surrounded by edematous stroma (left), and associated with clear cell borderline tumor with an adenofibromatous appearance (right).

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/
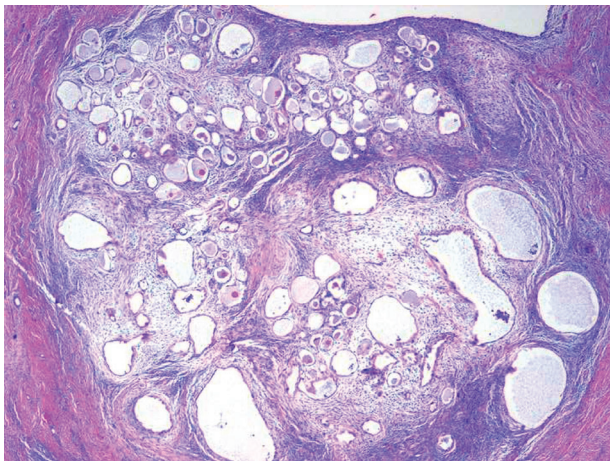
PR expression would likely be an endometrioid carcinoma, not a clear cell carcinoma (see the following). A carcinoma that expressed CK20 and CDX2 without CK7 or ER would support enteric differentiation, and diffuse p16 expression would suggest the possibility of a metastatic endocervical carcinoma.

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

FIG. 13. Clear cell carcinoma: microcystic pattern.

FIG. 15. Clear cell carcinoma resembling serous borderline tumor.

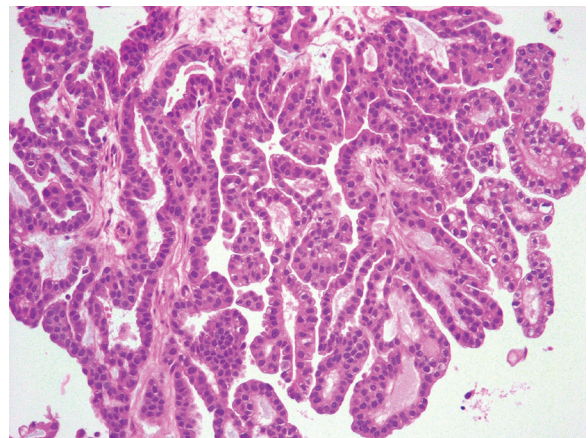**TABLE 10.** *Papillary tumors containing clear cells: low nuclear grade (112)*

Clear cell carcinoma (CCC)	Serous borderline tumor (SBT)
Unilateral	Bilateral
Nonhierarchical branching	Hierarchical branching
Monomorphous population	Mixed cell population
Hobnail cells	Pink cell tufts
At least focal atypia	Minimal atypia
Increased mitotic activity*	Low mitotic rate
Other CCC patterns	SBT patterns
Endometriosis	Serous cystadenoma
WT1−/ER−	WT1+/ER+

* indicates approximately 5 mitotic figures/high power fields.

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 hobnailed 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 clinicopathologic 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 confirmatory 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 borderline 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.

REFERENCES

1. Jaffe NS, ed. Pathology and Genetics: Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research in Cancer, 2003.
2. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med* 1996;335:1413–6.
3. Shaw PA, McLaughlin JR, Zweemer RP, et al. Histopathologic features of genetically determined ovarian cancer. *Int J Gynecol Pathol* 2002;21:407–11.
4. Singer G, Kurman RJ, Chang HW, et al. Diverse tumorigenic pathways in ovarian serous carcinoma. *Am J Pathol* 2002;160:1223–8.
5. Singer G, Stohr R, Cope L, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. *Am J Surg Pathol* 2005;29:218–24.
6. Sato N, Tsunoda H, Nishida M, et al. Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res* 2000;60:7052–6.
7. Dinulescu DM, Ince TA, Quade BJ, et al. Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer. *Nat Med* 2005;11:63–70.
8. Kato N, Sasou S, Motoyama T. Expression of hepatocyte nuclear factor-1beta (HNF-1beta) in clear cell tumors and endometriosis of the ovary. *Mod Pathol* 2006;19:83–9.
9. Korner M, Burckhardt E, Mazzucchelli L. Higher frequency of chromosomal aberrations in ovarian endometriosis compared to extragonadal endometriosis: a possible link to endometrioid adenocarcinoma. *Mod Pathol* 2006;19:1615–23.
10. Bell KA, Kurman RJ. A clinicopathologic analysis of atypical proliferative (borderline) tumors and well-differentiated endometrioid adenocarcinomas of the ovary. *Am J Surg Pathol* 2000;24:1465–79.

11. Roth LM, Emerson RE, Ulbright TM. Ovarian endometrioid tumors of low malignant potential: a clinicopathologic study of 30 cases with comparison to well-differentiated endometrioid adeno-carcinoma. *Am J Surg Pathol* 2003;27:1253–9.

12. Leitao MM, Boyd J, Hummer A, et al. Clinicopathologic analysis of early-stage sporadic ovarian carcinoma. *Am J Surg Pathol* 2004; 28:147–59.

13. Chen S, Leitao MM, Tornos C, et al. Invasion patterns in stage I endometrioid and mucinous ovarian carcinomas: a clinicopatho-logic analysis emphasizing favorable outcomes in carcinomas without destructive stromal invasion and the occasional malignant course of carcinomas with limited destructive stromal invasion. *Mod Pathol* 2005;18:903–11.

14. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II-IV low-grade serous carcinoma of the ovary. *Obstet Gynecol* 2006;108:361–8.

15. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer* 2000;88:2584–9.

16. Itamochi H, Kigawa J, Sugiyama T, et al. Low proliferation activity may be associated with chemoresistance in clear cell carcinoma of the ovary. *Obstet Gynecol* 2002;100:281–7.

17. Pectasides D, Fountzilas G, Aravantinos G, et al. Advanced stage clear-cell epithelial ovarian cancer: the Hellenic Cooperative Oncology Group experience. *Gynecol Oncol* 2006;102:285–91.

18. Goff BA, Sainz de la Cuesta R, Muntz HG, et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. *Gynecol Oncol* 1996;60:412–7.

19. Eltabbakh GH, Mount SL, Beatty B, et al. Clinical and molecular differences between clear cell and papillary serous ovarian carcinoma. *J Surg Oncol* 2006;93:379–86.

20. Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. *Am J Surg Pathol* 1999;23:617–35.

21. Lee KR, Scully RE. Mucinous tumors of the ovary: a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with 'pseudomyxoma peritonei'. *Am J Surg Pathol* 2000;24:1447–64.

22. Rodriguez IM, Prat J. Mucinous tumors of the ovary: a clinicopathologic analysis of 75 borderline tumors (of intestinal type) and carcinomas. *Am J Surg Pathol* 2002;26:139–52.

23. Hoerl HD, Hart WR. Primary ovarian mucinous cystadenocarci-nomas: a clinicopathologic study of 49 cases with long-term follow-up. *Am J Surg Pathol* 1998;22:1449–62.

24. Burks RT, Sherman ME, Kurman RJ. Micropapillary serous carcinoma of the ovary. A distinctive low-grade carcinoma related to serous borderline tumors. *Am J Surg Pathol* 1996;20:1319–30.

25. Seidman JD, Kurman RJ. Subclassification of serous borderline tumors of the ovary into benign and malignant types. A clinicopathologic study of 65 advanced stage cases. *Am J Surg Pathol* 1996;20:1331–45.

26. Prat J, De Nictolis M. Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. *Am J Surg Pathol* 2002;26:1111–28.

27. Eichhorn JH, Bell DA, Young RH, et al. Ovarian serous borderline tumors with micropapillary and cribriform patterns: a study of 40 cases and comparison with 44 cases without these patterns. *Am J Surg Pathol* 1999;23:397–409.

28. Deavers MT, Gershenson DM, Tortolero-Luna G, et al. Micro-papillary and cribriform patterns in ovarian serous tumors of low malignant potential: a study of 99 advanced stage cases. *Am J Surg Pathol* 2002;26:1129–41.

29. Longacre TA, McKenney JK, Tazelaar HD, et al. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (> or =5-year) follow-up. *Am J Surg Pathol* 2005;29:707–23.

30. Slomovitz BM, Caputo TA, Gretz HF 3rd, et al. A comparative analy-sis of 57 serous borderline tumors with and without a noninvasive micropapillary component. *Am J Surg Pathol* 2002;26:592–600.

31. 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.

32. Silverberg SG,. Histopathologic grading of ovarian carcinoma: a review and proposal. *Int J Gynecol Pathol* 2000;19:7–15.

33. Gynecologic Oncology Group. Available at: http://www.gog.org. Accessed November 30, 2007.

34. Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. *Int J Gynecol Pathol* 2004;23:41–4.

35. Che M, Tornos C, Deavers MT, et al. Ovarian mixed-epithelial carcinomas with a microcystic pattern and signet-ring cells. *Int J Gynecol Pathol* 2001;20:323–8.

36. Ulbright TM, Roth LM, Sutton GP. Papillary serous carcinoma of the ovary with squamous differentiation. *Int J Gynecol Pathol* 1990;9:86–94.

37. Horn LC, Hanel C, Bartholdt E, et al. Serous carcinoma of the endometrium with choriocarcinomatous differentiation: a case report and review of the literature indicate the existence of 2 prognostically relevant tumor types. *Int J Gynecol Pathol* 2006; 25:247–51.

38. Goldstein NS, Uzieblo A. WT1 immunoreactivity in uterine papillary serous carcinomas is different from ovarian serous carcinomas. *Am J Clin Pathol* 2002;117:541–5.

39. Egan JA, Ionescu MC, Eapen E, et al. Differential expression of WT1 and p53 in serous and endometrioid carcinomas of the endometrium. *Int J Gynecol Pathol* 2004;23:119–22.

40. Hwang H, Quenneville L, Yaziji H, et al. Wilms tumor gene product: sensitive and contextually specific marker of serous carcinomas of ovarian surface epithelial origin. *Appl Immunohis-tochem Mol Morphol* 2004;12:122–6.

41. Kupryjanczyk J, Thor AD, Beauchamp R, et al. p53 gene mutations and protein accumulation in human ovarian cancer. *Proc Natl Acad Sci U S A* 1993;90:4961–5.

42. Teneriello MG, Ebina M, Linnoila RI, et al. p53 and Ki-ras gene mutations in epithelial ovarian neoplasms. *Cancer Res* 1993;53: 3103–8.

43. DiCioccio RA, Werness BA, Peng R, et al. Correlation of TP53 mutations and p53 expression in ovarian tumors. *Cancer Genet Cytogenet* 1998;105:93–102.

44. Leitao MM, Soslow RA, Baergen RN, et al. Mutation and expression of the TP53 gene in early stage epithelial ovarian carcinoma. *Gynecol Oncol* 2004;93:301–6.

45. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin Cancer Res* 2004;10:2473–81.

46. Kashima K, Oite T, Aoki Y, et al. Screening of BRCA1 mutation using immunohistochemical staining with C-terminal and N-terminal antibodies in familial ovarian cancers. *Jpn J Cancer Res* 2000;91:399–409.

47. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 2006;30:230–6.

48. Carcangiu ML, Peissel B, Pasini B, et al. Incidental carcinomas in prophylactic specimens in BRCA1 and BRCA2 germ-line mutation carriers, with emphasis on fallopian tube lesions: report of 6 cases and review of the literature. *Am J Surg Pathol* 2006; 30:1222–30.

49. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol* 2006;100:58–64.

50. Colgan TJ. Challenges in the early diagnosis and staging of Fallopian-tube carcinomas associated with BRCA mutations. *Int J Gynecol Pathol* 2003;22:109–20.

51. Singer G, Oldt R 3rd, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst* 2003;95:484–6.

52. Shih IEM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. *Am J Pathol* 2004;164:1511–8.

53. Ho CL, Kurman RJ, Dehari R, et al. Mutations of BRAF and KRAS precede the development of ovarian serous borderline tumors. *Cancer Res* 2004;64:6915–8.

54. Dehari R, Kurman RJ, Logani S, et al. The development of high-grade serous carcinoma from atypical proliferative (borderline) serous tumors and low-grade micropapillary serous carcinoma: a morphologic and molecular genetic analysis. *Am J Surg Pathol* 2007;31:1007–12.

55. Bell DA, Longacre TA, Prat J, et al. Serous borderline (low malignant potential, atypical proliferative) ovarian tumors: workshop perspectives. *Hum Pathol* 2004;35:934–48.

56. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol* 2004;35:918–33.

57. Euscher ED, Malpica A, Deavers MT, et al. Differential expression of WT-1 in serous carcinoma in the peritoneum with or without associated serous carcinoma in endometrial polyps. *Am J Surg Pathol* 2005;29:1074–8.

58. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol* 2003;27:985–93.

59. Vang R, Gown AM, Barry TS, et al. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: analysis of coordinate immunohistochemical expression profiles and staining distribution in 179 cases. *Am J Surg Pathol* 2006;30:1130–9.

60. Ji H, Isacson C, Seidman JD, et al. Cytokeratins 7 and 20, Dpc4, and MUC5AC in the distinction of metastatic mucinous carcinomas in the ovary from primary ovarian mucinous tumors: Dpc4 assists in identifying metastatic pancreatic carcinomas. *Int J Gynecol Pathol* 2002;21:391–400.

61. Ronnett BM, Kurman RJ, Shmookler BM, et al. The morphologic spectrum of ovarian metastases of appendiceal adenocarcinomas: a clinicopathologic and immunohistochemical analysis of tumors often misinterpreted as primary ovarian tumors or metastatic tumors from other gastrointestinal sites. *Am J Surg Pathol* 1997;21:1144–55.

62. Ronnett BM, Shmookler BM, Diener-West M, et al. Immunohistochemical evidence supporting the appendiceal origin of pseudomyxoma peritonei in women. *Int J Gynecol Pathol* 1997;16:1–9.

63. Logani S, Oliva E, Arnell PM, et al. Use of novel immunohistochemical markers expressed in colonic adenocarcinoma to distinguish primary ovarian tumors from metastatic colorectal carcinoma. *Mod Pathol* 2005;18:19–25.

64. Elishaev E, Gilks CB, Miller D, et al. Synchronous and metachronous endocervical and ovarian neoplasms: evidence supporting interpretation of the ovarian neoplasms as metastatic endocervical adenocarcinomas simulating primary ovarian surface epithelial neoplasms. *Am J Surg Pathol* 2005;29:281–94.

65. Vang R, Gown AM, Barry TS, et al. Immunohistochemistry for estrogen and progesterone receptors in the distinction of primary and metastatic mucinous tumors in the ovary: an analysis of 124 cases. *Mod Pathol* 2006;19:97–105.

66. Cao D, Ji H, Ronnett BM. Expression of mesothelin, fascin, and prostate stem cell antigen in primary ovarian mucinous tumors and their utility in differentiating primary ovarian mucinous tumors from metastatic pancreatic mucinous carcinomas in the ovary. *Int J Gynecol Pathol* 2005;24:67–72.

67. Gemignani ML, Schlaerth AC, Bogomolniy F, et al. Role of KRAS and BRAF gene mutations in mucinous ovarian carcinoma. *Gynecol Oncol* 2003;90:378–81.

68. Enomoto T, Weghorst CM, Inoue M, et al. K-ras activation occurs frequently in mucinous adenocarcinomas and rarely in other common epithelial tumors of the human ovary. *Am J Pathol* 1991;139:777–85.

69. Young RH. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the Krukenberg tumor. *Adv Anat Pathol* 2006;13:205–27.

70. Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases. *Am J Surg Pathol* 2003;27:281–92.

71. Vang R, Gown AM, Farinola M, et al. p16 expression in primary ovarian mucinous and endometrioid tumors and metastatic adenocarcinomas in the ovary: utility for identification of metastatic HPV-related endocervical adenocarcinomas. *Am J Surg Pathol* 2007;31:653–63.

72. Irving JA, Young RH. Lung carcinoma metastatic to the ovary: a clinicopathologic study of 32 cases emphasizing their morphologic spectrum and problems in differential diagnosis. *Am J Surg Pathol* 2005;29:997–1006.

73. Young RH, Prat J, Scully RE. Ovarian endometrioid carcinomas resembling sex cord-stromal tumors. A clinicopathological analysis of 13 cases. *Am J Surg Pathol* 1982;6:513–22.

74. Roth LM, Liban E, Czernobilsky B. Ovarian endometrioid tumors mimicking Sertoli and Sertoli-Leydig cell tumors: Sertoliform variant of endometrioid carcinoma. *Cancer* 1982;50:1322–31.

75. Tornos C, Silva EG, Ordonez NG, et al. Endometrioid carcinoma of the ovary with a prominent spindle-cell component, a source of diagnostic confusion. A report of 14 cases. *Am J Surg Pathol* 1995;19:1343–53.

76. Moreno-Bueno G, Gamallo C, Perez-Gallego L, et al. Beta-Catenin expression pattern, beta-catenin gene mutations, and microsatellite instability in endometrioid ovarian carcinomas and synchronous endometrial carcinomas. *Diagn Mol Pathol* 2001;10:116–22.

77. Catasus L, Bussaglia E, Rodrguez I, et al. Molecular genetic alterations in endometrioid carcinomas of the ovary: similar frequency of beta-catenin abnormalities but lower rate of microsatellite instability and PTEN alterations than in uterine endometrioid carcinomas. *Hum Pathol* 2004;35:1360–8.

78. Irving JA, Catasus L, Gallardo A, et al. Synchronous endometrioid carcinomas of the uterine corpus and ovary: alterations in the beta-catenin (CTNNB1) pathway are associated with independent primary tumors and favorable prognosis. *Hum Pathol* 2005;36:605–19.

79. Oliva E, Sarrio D, Brachtel EF, et al. High frequency of beta-catenin mutations in borderline endometrioid tumours of the ovary. *J Pathol* 2006;208:708–13.

80. Acs G, Pasha T, Zhang PJ. WT1 is differentially expressed in serous, endometrioid, clear cell, and mucinous carcinomas of the peritoneum, fallopian tube, ovary, and endometrium. *Int J Gynecol Pathol* 2004;23:110–8.

81. Shimizu M, Toki T, Takagi Y, et al. Immunohistochemical detection of the Wilms' tumor gene (WT1) in epithelial ovarian tumors. *Int J Gynecol Pathol* 2000;19:158–63.

82. Caduff RF, Svoboda-Newman SM, Bartos RE, et al. Comparative analysis of histologic homologues of endometrial and ovarian carcinoma. *Am J Surg Pathol* 1998;22:319–26.

83. Wu R, Hendrix-Lucas N, Kuick R, et al. Mouse model of human ovarian endometrioid adenocarcinoma based on somatic defects in the Wnt/beta-catenin and PI3K/Pten signaling pathways. *Cancer Cell* 2007;11:321–33.

84. Wu R, Zhai Y, Fearon ER, et al. Diverse mechanisms of beta-catenin deregulation in ovarian endometrioid adenocarcinomas. *Cancer Res* 2001;61:8247–55.

85. Willner J, Wurz K, Allison KH, et al. Alternate molecular genetic pathways in ovarian carcinomas of common histological types. *Hum Pathol* 2007;38:607–13.

86. Longacre TA, Chung MH, Jensen DN, et al. Proposed criteria for the diagnosis of well-differentiated endometrial carcinoma. A diagnostic test for myoinvasion. *Am J Surg Pathol* 1995;19:371–406.

87. Kurman RJ, Norris HJ. Evaluation of criteria for distinguishing

atypical endometrial hyperplasia from well-differentiated carcinoma. *Cancer* 1982;49:2547–59.

88. Mizuno M, Kikkawa F, Shibata K, et al. Long-term follow-up and prognostic factor analysis in clear cell adenocarcinoma of the ovary. *J Surg Oncol* 2006;94:138–43.

89. Takano M, Kikuchi Y, Yaegashi N, et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. *Br J Cancer* 2006;94:1369–74.

90. Behbakht K, Randall TC, Benjamin I, et al. Clinical characteristics of clear cell carcinoma of the ovary. *Gynecol Oncol* 1998;70:255–8.

91. Yamamoto S, Tsuda H, Yoshikawa T, et al. Clear cell adenocarcinoma associated with clear cell adenofibromatous components: a subgroup of ovarian clear cell adenocarcinoma with distinct clinicopathologic characteristics. *Am J Surg Pathol* 2007;31:999–1006.

92. 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*. In press.

93. Silva EG, Young RH. Endometrioid neoplasms with clear cells: a report of 21 cases in which the alteration is not of typical secretory type. *Am J Surg Pathol* 2007;31:1203–8.

94. Kaneuchi M, Sasaki M, Tanaka Y, et al. WT1 and WT1-AS genes are inactivated by promoter methylation in ovarian clear cell adenocarcinoma. *Cancer* 2005;104:1924–30.

95. Waldstrom M, Grove A. Immunohistochemical expression of wilms tumor gene protein in different histologic subtypes of ovarian carcinomas. *Arch Pathol Lab Med* 2005;129:85–8.

96. Hwang H, Quenneville L, Yaziji H, et al. Wilms tumor gene product: sensitive and contextually specific marker of serous carcinomas of ovarian surface epithelial origin. *Appl Immunohistochem Mol Morphol* 2004;12:122–6.

97. Koshiyama M, Konishi I, Mandai M, et al. Immunohistochemical analysis of p53 protein and 72 kDa heat shock protein (HSP72) expression in ovarian carcinomas. Correlation with clinicopathology and sex steroid receptor status. *Virchows Arch* 1995;425:603–9.

98. Shimizu M, Nikaido T, Toki T, et al. Clear cell carcinoma has an expression pattern of cell cycle regulatory molecules that is unique among ovarian adenocarcinomas. *Cancer* 1999;85:669–77.

99. Otis CN, Krebs PA, Quezado MM, et al. Loss of heterozygosity in P53, BRCA1, and estrogen receptor genes and correlation to expression of p53 protein in ovarian epithelial tumors of different cell types and biological behavior. *Hum Pathol* 2000;31:233–8.

100. Lee S, Garner EI, Welch WR, et al. Over-expression of hypoxia-inducible factor 1 alpha in ovarian clear cell carcinoma. *Gynecol Oncol* 2007;106:311–7.

101. Lin F, Zhang PL, Yang XJ, et al. Human kidney injury molecule-1 (hKIM-1): a useful immunohistochemical marker for diagnosing renal cell carcinoma and ovarian clear cell carcinoma. *Am J Surg Pathol* 2007;31:371–81.

102. Yamamoto S, Tsuda H, Aida S, et al. Immunohistochemical detection of hepatocyte nuclear factor 1beta in ovarian and endometrial clear-cell adenocarcinomas and nonneoplastic endometrium. *Hum Pathol* 2007;38:1074–80.

103. Tsuchiya A, Sakamoto M, Yasuda J, et al. Expression profiling in ovarian clear cell carcinoma: identification of hepatocyte nuclear factor-1 beta as a molecular marker and a possible molecular target for therapy of ovarian clear cell carcinoma. *Am J Pathol* 2003;163:2503–12.

104. Stadlmann S, Gueth U, Baumhoer D, et al. Glypican-3 expression in primary and recurrent ovarian carcinomas. *Int J Gynecol Pathol* 2007;26:341–4.

105. Otsuka J, Okuda T, Sekizawa A, et al. K-ras mutation may promote carcinogenesis of endometriosis leading to ovarian clear cell carcinoma. *Med Electron Microsc* 2004;37:188–92.

106. Amemiya S, Sekizawa A, Otsuka J, et al. Malignant transformation of endometriosis and genetic alterations of K-ras and microsatellite instability. *Int J Gynaecol Obstet* 2004;86:371–6.

107. Ueda H, Watanabe Y, Nakai H, et al. Microsatellite status and immunohistochemical features of ovarian clear-cell carcinoma. *Anticancer Res* 2005;25:2785–8.

108. Cai KQ, Albarracin C, Rosen D, et al. Microsatellite instability and alteration of the expression of hMLH1 and hMSH2 in ovarian clear cell carcinoma. *Hum Pathol* 2004;35:552–9.

109. Gras E, Catasus L, Arguelles R, et al. Microsatellite instability, MLH-1 promoter hypermethylation, and frameshift mutations at coding mononucleotide repeat microsatellites in ovarian tumors. *Cancer* 2001;92:2829–36.

110. Roth LM, Langley FA, Fox H, et al. Ovarian clear cell adenofibromatous tumors. Benign, of low malignant potential, and associated with invasive clear cell carcinoma. *Cancer* 1984;53:1156–63.

111. Bell DA, Scully RE. Benign and borderline clear cell adenofibromas of the ovary. *Cancer* 1985;56:2922–31.

112. Sangoi AR, Soslow RA, Teng NN, et al. Ovarian papillary clear cell carcinoma: a potential mimic of serous tumor of low malignant potential. *Am J Surg Pathol*. In press.

113. 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.

114. Gershenson DM, Baker VV, Price JE, et al. Molecular profile of advanced-stage transitional cell carcinoma of the ovary. *Am J Obstet Gynecol* 1997;177:120–5.

115. Kommoss F, Kommoss S, Schmidt D, et al. Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom. 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.

116. Robey SS, Silva EG, Gershenson DM, et al. Transitional cell carcinoma in high-grade high-stage ovarian carcinoma. An indicator of favorable response to chemotherapy. *Cancer* 1989;63:839–47.

117. Silva EG, Robey-Cafferty SS, Smith TL, et al. Ovarian carcinomas with transitional cell carcinoma pattern. *Am J Clin Pathol* 1990;93:457–65.

118. Costa MJ, Hansen C, Dickerman A, et al. Clinicopathologic significance of transitional cell carcinoma pattern in nonlocalized ovarian epithelial tumors (stages 2-4). *Am J Clin Pathol* 1998;109:173–80.

119. Eichhorn JH, Young RH. Transitional cell carcinoma of the ovary: a morphologic study of 100 cases with emphasis on differential diagnosis. *Am J Surg Pathol* 2004;28:453–63.

120. Shappell HW, Riopel MA, Smith Sehdev AE, et al. Diagnostic criteria and behavior of ovarian seromucinous (endocervical-type mucinous and mixed cell-type) tumors: atypical proliferative (borderline) tumors, intraepithelial, microinvasive, and invasive carcinomas. *Am J Surg Pathol* 2002;26:1529–41.

121. Vang R, Gown AM, Barry TS, et al. Ovarian atypical proliferative (borderline) mucinous tumors: gastrointestinal and seromucinous (endocervical-like) types are immunophenotypically distinctive. *Int J Gynecol Pathol* 2006;25:83–9.

122. Rutgers JL, Scully RE. Ovarian mixed-epithelial papillary cystadenomas of borderline malignancy of mullerian type. A clinicopathologic analysis. *Cancer* 1988;61:546–54.

123. Rutgers JL, Scully RE. Ovarian mullerian mucinous papillary cystadenomas of borderline malignancy. A clinicopathologic analysis. *Cancer* 1988;61:340–8.

124. Altrabulsi B, Malpica A, Deavers MT, et al. Undifferentiated carcinoma of the endometrium. *Am J Surg Pathol* 2005;29:1316–21.