Strategies for Classifying Endometrial Carcinoma with Clear Cells

Oluwole Fadare, MD
University of California San Diego, San Diego, CA
Email: ofadare@ucsd.edu

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Introduction:

Clear cell carcinomas (CCC) is one of the rarest forms of endometrial carcinoma. In one series of 852 consecutive endometrial carcinomas managed at a single academic center, only 3 (0.35%) were considered to be CCC (1). Although CCC is rare, it features frequently in the differential diagnosis of endometrial neoplasms, primarily because one of the morphologic features of CCC - the presence of clear cells - is not specific to the histotype. CCC is considered a high grade histotype, hence the necessity of their separation from low grade endometrial carcinomas. However, CCC should also be distinguished from other high grade histotypes because there may be prognostic (2-4) and therapeutic differences (3,5), and due to the possibility that CCC is associated with a comparatively increased risk of thromboembolic events (6,7). Additionally, erroneous pathologic classifications of non-CCC histotypes as CCC not only represents a significant impediment to scientific advancement on both histotypes, but also may deny some patients eligibility for potentially life-saving clinical trials to which they should qualify. Presented herein is an approach to the pathologic classification of endometrial carcinomas with clear cells, with an emphasis on the distinction of CCC from its potential histologic mimics.

Pathologic features of clear cell carcinoma:

The 3 classically-defined architectural patterns of CCC are solid, papillary and tubulocystic, and most cases show an admixture of patterns (8-10). The papillary pattern is characteristically defined by a combination of small rounded papillae and other non-specific papillae. Small rounded papillae are rounded structures that may protrude into a gland or cyst, or may be an end tributary of a non-specific structure. Their stromal cores may be hyalinized, edematous, notably inflamed, or non-specifically fibroblastic. Other papillary patterns show non-specific architectures with varying degrees of hierarchical branching. The tubulocystic pattern represents a spectrum of acinar units that may range from small open glands, closed tubular units, to large open cysts. Confluence may or may not be present. The solid pattern is characterized by cells with well-defined cell membranes and clear to eosinophilic cytoplasm. Glands and papillae are lined by cells that may be polygonal with clear and/or eosinophilic cytoplasm, hobnail, or flat. Columnar cells are typically not diffusely present, and neither should stratification more than 3 cells thick. Pleomorphism is usually moderate, although patchy zones of severe atypia or notable cytologic blandness may be seen. Most CCC have a mitotic index of less than 10 MF/10 HPF. Squamous differentiation is absent. Eosinophilic, targetoid or psammoma bodies are not

uncommonly seen, but none are histotype-specific. 67-93% of CCC are positive for Napsin A, 67-100% are positive for hepatocyte nuclear factor 1-beta (HNF1β), 7-21% are positive for the estrogen receptor (ER), and 6-45% are positive for the progesterone receptor (PR). Approximately one-third of CCC show mutation pattern p53 staining, and most cases are diffusely positive for p16 (11-27). Two studies have found AMACR (α-methylacyl-coenzyme-A racemase or p504s), to be frequently positive in müllerian CCC, although its specificity requires further study (28,29). Accordingly, the typical immunohistochemical profile of CCC is Napsin A [+], HNF1β [+], ER [-], and PR [-]. However, significant subsets of cases deviate from this basic profile regarding one or more of these markers.

Endometrial tumors with clear cells:

The diagnosis of CCC is based on its distinctive combination of architectural and cytologic features, as described above. However, cells with cytoplasmic clarity may be seen across a wide spectrum of uterine neoplasms, including epithelioid mesenchymal tumors (such as epithelioid smooth muscle tumors, epithelioid endometrial stromal tumors, and perivascular epithelioid cell tumors), metastatic carcinoma (especially metastatic renal cell carcinoma), metastatic melanomas, trophoblastic tumors (including choriocarcinomas, epithelioid trophoblastic tumors and placental site trophoblastic tumors), another germ cell-type tumor (yolk sac tumors of the endometrium), and most histotypes of uterine carcinoma (30). Accordingly, the first task when faced with a neoplasm with a significant clear cell population is to accurately categorize it into a broad diagnostic group to which it belongs. The following section will focus primarily on endometrial carcinomas, with only a limited discussion of non-epithelial entities. 3 histologic patterns will be discussed.

a) **Architecturally complex glands or papillae lined by columnar cells with subnuclear and/or supranuclear vacuolization**: Architecturally complexity is defined here by extensive glandular confluence, complex papillation, cribriform formation or other patterns of intraglandular complexity. First, it must be ascertained that apparent subnuclear and/or supranuclear vacuolization is not mucinous change, an alteration to which it may bear some superficial similarity. This can usually be accomplished by careful inspection of morphologic features, although histochemical studies for mucin may buttress diagnostic certainty. Also worthy of consideration *a priori*, especially in sampling specimens, is the possibility that the proliferation is a hyperplasia with secretory change (31-34), rather than a carcinoma. Although atypical hyperplasia with secretory change is potentially associated with diminution in atypia and mitotic activity, in general, they are distinguished from carcinoma using the same criteria that are applicable for conventional (non-secretory) hyperplasia (35). Endometrioid carcinoma with secretory differentiation (so-called “secretory carcinoma”) is most commonly comprised of tubular glands lined by columnar cells with subnuclear and/or supranuclear clarity, and relatively monomorphic oval nuclei that may be pseudostratified (36-39). Some cases have a component of villoglandular-type papillae or, more rarely, solid component. Endometrioid carcinomas with secretory differentiation are distinguished from clear cell carcinoma because they lack the distinctive cytoarchitecture of CCC. They are devoid of tubulocystic patterns or the most common papillary pattern (small rounded papillae) of CCC. They are lined by columnar cells whereas CCC are lined by polygonal, cuboidal, hobnail or flat cells. Both may show a low

mitotic index. CCC usually displays higher levels of atypia than endometrioid carcinoma with secretory differentiation (36-39). By immunohistochemistry, endometrioid carcinomas with secretory differentiation are diffusely positive for ER and PR and are negative for Napsin A. Since CCC typically displays the opposite phenotype, that panel may be diagnostically useful. HNF1β was expressed focally in 1 (33%) of 3 secretory carcinomas in one series, as compared with 73% of CCC (23).

Endometrioid carcinoma with secretory differentiation should also distinguished from yolk sac tumors (YST) of the endometrium (40-44), a tumor with which it displays some morphologic overlap. YST commonly shows an admixture of histologic patterns, with the glandular pattern being one of the 2 commonest patterns (41). In the glandular pattern, glands and papillae may potentially be lined by columnar cells with nuclei that may be pseudostratified, and with varying amounts of supranuclear and/or subnuclear vacuolization. Accordingly, they are most likely to be mistaken for endometrioid carcinoma with secretory differentiation. Some subtle differences between these entities are discernable at the morphologic level: The vacuolation and nuclear location in YST are more haphazard than is typically seen in endometrioid carcinoma, giving a less “organized” appearance; the nuclei in YST have a more “primitive” appearance, with coarse chromatin; other histologic pattern that are more easily associable with YST, such as microcystic/reticular pattern, may be admixed (41). However, diagnostic errors in this differential diagnosis are best minimized by a general awareness and consideration of YST whenever the diagnosis of endometrioid carcinoma with secretory differentiation is a possibility, so that appropriate immunohistochemical studies may be performed. The latter should always be a multi-antibody panel that includes markers that are expected to be diffusely positive in low grade endometrioid carcinomas and negative in YST (such as ER, PAX8, CK7), and markers that are expected to show the converse phenotype (such as Glypican 3, AFP, SALL4), with the full understanding that many of these markers display no more than 60-70% sensitivity or specificity, even in this specific diagnostic scenario (41,42). Schiller-Duval bodies are only seen in a minority of YST (41), which limits their diagnostic utility, whereas eosinophilic and targetoid bodies may be seen in both.

YST may also display a morphologic overlap with CCC. This is attributable to 3 factors: 1) YST may display a sizable population of clear cells, 2) in the microcystic/reticular pattern, degeneration of myxoid areas may leave stromal mounds that are lined by a unilayer of cells with hobnail-like appearance, and 3) in the glandular pattern, epithelial cells may be more cuboidal than columnar, and may line small papillae. This overlap may be accentuated in a limited sample, where there is less background tumoral tissue to contextualize primary findings. Immunohistochemistry may be diagnostically useful in this scenario. Napsin A is negative in YST based on an assessment of a limited number of cases (41) whereas CCC are usually Napsin A positive (19). In contrast, CK7 and PAX8 are diffusely positive in CCC and are typically negative or focally positive in YST (41). Markers such as SALL4, AFP and Glypican 3, typically positive in YST and negative or limited-positive in CCC, are best utilized as part of a larger panel, since

information on their reactivities in CCC are somewhat limited at present time. Both CCC and YST frequently express HNF1β and both are usually negative for ER and PR.

Rarely, serous carcinoma, which can be lined by columnar cells in large areas of the tumor, may showed significant subnuclear vacuolization. These rare cases deviate from the classic morphologic profile of the histotype only by the aforementioned cytoplasmic vacuolization, and as such are easily recognized as serous carcinomas. The topic of clear cells in serous carcinoma is discussed in more detail below. Additionally, in a phenomenon that is more recognized in the ovary (45), but which the author has rarely encountered in the uterus, metastatic adenocarcinomas from the GI tract may show a significant population of cells with supranuclear and/or subnuclear vacuolization.

b) **Architecturally complex glands or papillae lined by columnar cells with or without clear cells, mixed with foci of solid clear cells**: The principal differential diagnostic considerations for this pattern includes endometrioid carcinoma with clear cells, mixed endometrioid-clear cell carcinoma, and clear cell carcinoma. Two broad guiding principles are worthy of consideration for tumors that display this pattern: 1) given the frequencies of these histotypes, in a tumor that otherwise displays features of endometrioid carcinoma, the presence of clear cells is substantially more likely to represent a morphologic variation rather than a true CCC component; 2) According to WHO guidelines, in a true mixed endometrioid/clear carcinoma, the minor component must constitute at least 5% of the tumor, from which it is usually spatially distinct. Each component should be recognizable on H & E preparations, and if viewed in isolation, should display a full complement of morphologic and/or immunophenotypic features that is consistent with the proposed histotype (61).

Endometrioid carcinoma with clear cells: Clear cell change in endometrioid carcinomas, other than the aforementioned secretory-type change, fall into 2 broad groups: endometrioid carcinoma with glycogenation in foci of squamous differentiation, and endometrioid carcinoma with diffuse clear cells in glandular and/or solid areas from unknown causes (clear cell change NOS). The former is the most common cause of clear cell change in endometrial carcinomas, in the author's experience. The myriad of patterns and appearances that may be associated with squamous differentiation in endometrioid carcinoma are reviewed in detail elsewhere (46,47). These may be in the form of solid plaques of squamous epithelium, apparently infiltrative solid nests of squamous epithelium likely borne out of completely replaced glands, larger glands or papillae partially replaced by squamous epithelium, resulting in a variety of solid or filiform architectures, and the more conventional intraglandular squamous morules. All of these patterns may be associated with significant glycogenation. Associated glands for any of these patterns may also display cytoplasmic clarity in a secretory or non-secretory pattern. The differential diagnosis is accordingly a mixed endometrioid/clear cell carcinoma or a pure endometrioid carcinoma. Foci of squamous differentiation are recognizable by: 1) direct transitions between the glycogenated areas and non-glycogenated (conventional) areas of squamous differentiation; 2) morphologic features of squamous differentiation, such as squamous-type intercellular junctions or keratinization provide supportive evidence but are

insensitive; 3) direct morphologic transitions between the glycogenated solid nests and endometrioid-type glands would be inconsistent with a mixed endometrioid/clear cell carcinoma; and 4) In true mixed carcinoma, the endometrioid areas and clear cell areas are typically discrete, and are typically devoid of the close admixture of squamous elements and endometrioid-type glands seen in endometrioid carcinoma with squamous differentiation. Of note, immunohistochemical markers for squamous differentiation (such as p40, p63, and CK 5/6) have no more than a moderate specificity and a low sensitivity in this differential diagnosis. This is because a significant subset of both endometrioid and clear cell carcinoma may show a population of cells that are positive for these markers, which limits their specificity (48,49). Sensitivity is similarly suboptimal because squamous-type differentiation in endometrioid carcinoma may be an admixture of morular and non-morular forms, and morular forms are known to be negative or only weakly immunoreactive for these markers (50-52).

Other forms of clear cell change in endometrioid carcinoma, other than the secretory type or those borne out of glycogenated squamous epithelium, may be seen. These morphologic alterations are variable, may be from lipidization, altered mucin, hydropic change, less recognized forms of glycogenation, or unknown factors (36). Most tumors show other features that render them easily recognizable as endometrioid carcinomas given an awarenesss of these potential morphologic variations. A variety of appearances may be seen, including constituent columnar cells with abundant cytoplasm, small nuclei and a generalized cytoplasmic clarity that is more striking than is typically seen in secretory carcinoma. Tumor cells may also be seen that are more cuboidal than columnar, but these usually form a minority population and transition to more conventional areas. A distinctive vacuolized pattern may also be encountered, with empty cytoplasmic vacuoles in both the glandular, solid, and morular elements of an otherwise typical endometrioid carcinoma. An iatrogenic form of cytoplasmic clarity may be seen in endometrioid carcinoma treated with strong progestins. Foci of clear cell metaplasia in this setting do not typically pose diagnostic difficulty given the clinicopathologic context. However, Arias-Stella reaction may also be seen in direct association with progestin-treated endometrioid carcinomas, resulting in foci of striking nucleomegaly, hyperchromasia and cytoplasmic clarity that can result in an erroneous interpretation of a clear cell carcinoma component (53). Furthermore, these foci are immunoreactive for Napsin A if using the widely-employed polyclonal antibody (54). Helpful diagnostic clues include the clinical history, the presence of squamous morules or other metaplastic changes within the foci of Arias-Stella reaction, the absence of mitotic figures therein, and morphologic transitions to glands of more conventional endometrioid carcinoma. Another rare phenomenon, possibly having an iatrogenic basis, is hobnail alteration in endometrioid carcinoma. Typically identified in resection specimens, areas of hobnail change are almost invariably focal or patchy, which facilitates their recognition. Isolated glands that are half lined by columnar cells and half lined by hobnail cells also provide additional evidence that this is likely a metaplastic phenomenon. This alteration may be related to the pre-hysterectomy biopsy or curettage.

One potential diagnostic problem occurs when an otherwise low grade endometrioid carcinoma shows significant solid areas comprised of clear cells that are not morphologically consistent with squamous differentiation. The differential diagnosis again is a grade II or III endometrioid carcinoma versus a mixed grade I endometrioid carcinoma/clear cell carcinoma (46). First, the glandular component in the former frequently shows a secretory pattern as previously described, and these glandular areas typically merge with the solid areas. Indeed, a careful inspection of the apparently solid areas may reveal abortive or poorly formed acinar units. The solid areas of grade III endometrioid carcinoma also frequently shows a vaguely nested configuration. The solid and glandular areas show very comparable levels of nuclear abnormalities, which is typically closer to the lower end of the spectrum. The shared cytoplasmic clarity between the glandular and solid areas and direct morphologic transitions between them provides supportive evidence that these are components of the same histotype. A minority of cases show squamous differentiation. The tubulocystic and papillary patterns of typical CCC are absent in cases of true endometrioid carcinoma with this pattern. Immunohistochemistry may be useful to establish the line of differentiation of the solid areas, since they should not display a CCC-like immunophenotype. However, it should be noted that the solid areas in endometrioid carcinoma, irrespective of whether or not they display cytoplasmic clarity, commonly display a significant diminution of ER and PR expression relative to the glandular areas (17), and up to a third of cases show mutation-pattern p53 expression and diffuse p16 overexpression (55,56). This potential for a somewhat discrepant immunophenotypic profile between the glandular and solid areas is not necessarily evidence that they represent different histotypes.

c) **Solid clear cells**: In rare instances, an endometrial tumor is comprised entirely of solid proliferation of clear cells or cells with clear to eosinophilic cytoplasm. This is the pattern wherein a broad differential diagnosis *a priori* is most necessary. Esoteric considerations, such as epithelioid mesenchymal tumors (e.g epithelioid smooth muscle tumors, epithelioid endometrial stromal tumors, perivascular epithelioid cell tumors, etc), metastatic carcinoma (especially metastatic renal cell carcinoma), metastatic melanomas, trophoblastic tumors (including choriocarcinomas, epithelioid trophoblastic tumors and placental site trophoblastic tumors), solid-patterned yolk sac tumors of the endometrium, should be carefully excluded. If the case is determined to be a carcinoma, the possibility of metastatic clear cell renal cell carcinoma(CC-RCC) (57-60), which can rarely present in the uterus (59,60), should be considered. A clinical history of a renal mass or of renal cancer is clearly an important diagnostic factor. Microscopically, alveolar nests or solid sheets of clear cells are seen, some with inter-alveolar capillaries. Although this alveolar pattern is diagnostically helpful, its presence is not conclusive evidence in favor of CC-RCC over müllerian CCC. Cytoplasmic clarity may not be as prominent as would be expected in the kidney. Immunohistochemical markers are of significant utility in this context: In one study, CK7 and AMACR (positive in CCC, negative in CC-RCC), kidney-specific cadherin, renal cell carcinoma antigen and carbonic anhydrase (positive in CC-RCC, negative in CCC), were most useful in distinguishing CCC and CC-RCC. HNF1β, PAX8 and Napsin A are positive in both CCC and CC-RCC, and are accordingly non-discriminatory (60).

For primary endometrial carcinomas that are exclusively solid-patterned and comprised of clear cells with well-defined cell membranes, the differential diagnosis is most likely CCC, grade III endometrioid carcinoma, or very rarely, other histotypes. A purely solid proliferation of clear carcinomatous cells would be difficult to confidently histotype in the absence of glandular or papillary elements, or of morphologic markers of a specific histotype, such as squamous differentiation for an endometrioid carcinoma. The solid areas of grade III endometrioid carcinoma frequently but not invariably shows a vaguely nested configuration. It is uncommon for a true CCC to be entirely of the solid pattern, even in sampling specimens. In one study of 50 cases of CCC, the solid pattern was present at least focally in 27 (54%) of 50 cases, but was predominant in 9 (18%), and was the exclusive pattern in only 1 case (8). Parenthetically, the solid areas in CCC tend to show a higher mitotic index and more easily discernable nuclear anaplasia than the tubulocystic or papillary areas (8). Neither the prominence of the intercellular membranes nor the cytoplasmic location of nuclei (central versus near-membrane) reliably distinguishes solid-pattern endometrioid from solid-patterned clear cell carcinoma. As such, IHC is necessary to demonstrate a CCC-like phenotype in this scenario.

d) **Tumors with features of serous carcinoma as well as clear cells**: The differential diagnosis for this pattern includes serous carcinoma and mixed clear cell/serous carcinoma. True mixed serous/clear carcinomas should have components that are recognizable on H & E sections, and each component, if viewed in isolation, should display a complement of morphologic and/or immunophenotypic features that are fully consistent with the proposed histotype (61). Since clear cells are not in and of themselves diagnostic of CCC, their presence cannot be a sole basis for assigning a CCC-component to a tumor whose features are otherwise diagnostic of serous carcinoma (62). In ovarian carcinomas, where histotyping is more reproducible than in the uterus (63-65), serous carcinomas with clear cell features and mixed serous and clear cell carcinomas have a morphologic, immunophenotypic and molecular profile that is more consistent with serous than clear cell carcinomas (66-68). Clear cell change in serous carcinomas may appear as cytoplasmic vacuoles or diffuse cytoplasmic clarity. Extrauterine deposits may display more cytoplasmic clarity than the primary tumor. Such tumors nonetheless retain the other morphologic and most of the immunophenotypic features of serous carcinoma (61). At present time, there is no evidence that serous carcinomas with clear cells have any specific clinical significance.

e) Histotypically ambiguous carcinomas with clear cell and serous features: The interobserver variability that exists in the histotyping of high grade endometrial carcinomas is at least partially attributable to the existence of histotypically ambiguous tumors in the morphologic spectrum between serous and clear cell carcinomas (69,70). As was previously noted, the presence of clear cells in an otherwise classical serous carcinoma is not a sufficient reason to alter that primary classification. However, there are undoubtedly some tumors that defy easy categorization. Apparent histotypic ambiguity in a significant subset of these tumors, and possibly the great majority of them, likely represents a manifestation of variant morphology for one of the histotypes. However, morphologic criteria to reproducibly categorize the cases in the

middle of this spectrum are lacking. Immunohistochemical markers should be applied with caution in this setting, should invariably be used as a ">1-marker " panel, and should be used more for the high *negative predictive value* (of a given marker for a particular histotype) than for their *specificity*. For example, if the differential diagnosis is between CCC and serous carcinoma, a lack of expression of HNF1β and Napsin A argues against a CCC whereas a p53 wild-type phenotype argues against serous carcinoma. However, given the suboptimal information available on their specificity, positive expression for any of these markers has to be carefully weighed against all other aspects of the morphologic and immunophenotypic data, which are not infrequently incongruent. Most studies on potentially discriminatory immunohistochemical markers were performed on classical examples of the histotypes, and their diagnostic performance in ambiguous cases is not entirely clear. Overall, our approach is to strictly adhere to WHO guidelines on diagnosing mixed carcinomas, recognize the full morphologic and immunophenotypic spectrum for the clear cell and serous histotypes, as well as areas of potential morphologic overlap between them (hobnail cells, patchy areas of anaplasia, mutation-pattern p53 staining, stromal hyalinization, clear cells), and if a case can still not be classified, report it descriptively as a high grade carcinoma with an explanatory comment.

References:

1. Lewis GH, Folkins AK, Kong CS, Kempson RL, Longacre TA. Endometrial Clear Cell Carcinoma: Incidence and Clinicopathologic Features. Poster Session. United States and Canadian Academy of Pathology 101st Annual Meeting, Baltimore, March 2013
2. Altman AD, Ferguson SE, Atenafu EG, Köbel M, McAlpine JN, Panzarella T, Lau S, Gien LT, Gilks B, Clarke B, Cameron A, Nelson G, Han G, Samouëlian V, Ho TC, Louie K, Bernardini MQ. Canadian high risk endometrial cancer (CHREC) consortium: analyzing the clinical behavior of high risk endometrial cancers. Gynecol Oncol. 2015;139:268-74.
3. Bernardini MQ, Gien LT, Lau S, Altman AD, Gilks B, Ferguson SE, Köbel M, Samouëlian V, Wesa M, Cameron A, Nelson G, Han G, Clarke B, Ho TC, Panzarella T, Atenafu EG, McAlpine JN. Treatment related outcomes in high-risk endometrial carcinoma: Canadian high risk endometrial cancer consortium (CHREC). Gynecol Oncol. 2016;141:148-54.
4. Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, Powell MA, Hendrickson MR, Kapp DS, Chan JK. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642-6.
5. Olawaiye AB, Boruta DM 2nd. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;113:277-83.
6. Fadare O, Renshaw IL, Liang SX. Expression of tissue factor and heparanase in endometrial clear cell carcinoma: possible role for tissue factor in thromboembolic events. Int J Gynecol Pathol. 2011;30:252-61.
7. Lee L, Garrett L, Lee H, Oliva E, Horowitz N, Duska LR. Association of clear cell carcinoma of the endometrium with a high rate of venous thromboembolism. J Reprod Med. 2009;54:133-8.
8. Fadare O, Zheng W, Crispens MA, Jones HW, Khabele D, Gwin K, Liang SX, Mohammed K, Desouki MM, Parkash V, Hecht JL. Morphologic and other clinicopathologic features of endometrial clear cell carcinoma: a comprehensive analysis of 50 rigorously classified cases. Am J Cancer Res. 2013;3:70-95.
9. Kurman RJ, Scully RE. Clear cell carcinoma of the endometrium: an analysis of 21 cases. Cancer. 1976;37:872-82.
10. Silverberg SG, De Giorgi LS. Clear cell carcinoma of the endometrium. Clinical, pathologic, and ultrastructural findings. Cancer. 1973;31:1127-40.
11. Han G, Sidhu D, Duggan MA, Arseneau J, Cesari M, Clement PB, Ewanowich CA, Kalloger SE, Köbel M. Reproducibility of histological cell type in high-grade endometrial carcinoma. Mod Pathol. 2013;26:1594-604.
12. Han G, Soslow RA, Wethington S, Levine DA, Bogomolniy F, Clement PB, Köbel M, Gilks B, DeLair D. Endometrial Carcinomas With Clear Cells: A Study of a Heterogeneous Group of Tumors Including Interobserver Variability, Mutation Analysis, and Immunohistochemistry With HNF-1β. Int J Gynecol Pathol. 2015;34:323-33.
13. Hoang LN, Han G, McConechy M, Lau S, Chow C, Gilks CB, Huntsman DG, Köbel M, Lee CH. Immunohistochemical characterization of prototypical endometrial clear cell carcinoma--diagnostic utility of HNF-1β and oestrogen receptor. Histopathology. 2014;64:585-96.
14. Fadare O, Gwin K, Desouki MM, Crispens MA, Jones HW 3rd, Khabele D, Liang SX, Zheng W, Mohammed K, Hecht JL, Parkash V. The clinicopathologic significance of p53 and BAF-250a (ARID1A) expression in clear cell carcinoma of the endometrium. Mod Pathol. 2013;26:1101-10.
15. Bae HS, Kim H, Young Kwon S, Kim KR, Song JY, Kim I. Should endometrial clear cell carcinoma be classified as Type II endometrial carcinoma? Int J Gynecol Pathol. 2015;34:74-84.
16. Delair D, Soslow R. Endometrial clear cell carcinoma with and without aberrant p53 expression: a study of 16 cases [abstract] Mod Pathol. 2012;25(Suppl 2):265A.
17. Lim D, Ip PP, Cheung AN, Kiyokawa T, Oliva E. Immunohistochemical Comparison of Ovarian and Uterine Endometrioid Carcinoma, Endometrioid Carcinoma With Clear Cell Change, and Clear Cell Carcinoma. Am J Surg Pathol. 2015;39:1061-9.
18. Iwamoto M, Nakatani Y, Fugo K, Kishimoto T, Kiyokawa T. Napsin A is frequently expressed in clear cell carcinoma of the ovary and endometrium. Hum Pathol. 2015;46:957-62
19. Fadare O, Desouki MM, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Parkash V, Hecht JL. Frequent expression of Napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. Am J Surg Pathol. 2014;38:189-96.
20. Hoang LN, McConechy MK, Meng B, McIntyre JB, Ewanowich C, Gilks CB, Huntsman DG, Köbel M, Lee CH. Targeted mutation analysis of endometrial clear cell carcinoma. Histopathology. 2015;66:664-74.
21. Kim MY, Go H, Koh J, Lee K, Min HS, Kim MA, Jeon YK, Lee HS, Moon KC, Park SY, Kim WH, Chung DH. Napsin A is a useful marker for metastatic adenocarcinomas of pulmonary origin. Histopathology. 2014;65:195-206.
22. Yamamoto S, Tsuda H, Aida S, Shimazaki H, Tamai S, Matsubara O. Immunohistochemical detection of hepatocyte nuclear factor 1beta in ovarian and endometrial clear-cell adenocarcinomas and nonneoplastic endometrium. Hum Pathol. 2007;38:1074-80.
23. Fadare O, Liang SX. Diagnostic utility of hepatocyte nuclear factor 1-beta immunoreactivity in endometrial carcinomas: lack of specificity for endometrial clear cell carcinoma. Appl Immunohistochem Mol Morphol. 2012;20:580-7.
24. Reid-Nicholson M, Iyengar P, Hummer AJ, Linkov I, Asher M, Soslow RA. Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Mod Pathol. 2006;19:1091-100.
25. Mhawech-Fauceglia P, Yan L, Liu S, Pejovic T. ER+ /PR+ /TFF3+ /IMP3- immunoprofile distinguishes endometrioid from serous and clear cell carcinomas of the endometrium: a study of 401 cases. Histopathology. 2013;62:976-85.
26. Holmes BJ, Ronnett BM, Seidman JD, Yemelyanova A. Napsin A. A Sensitive Immunohistochemical Marker for Uterine Clear Cell Carcinoma [Abstract]. Mod Pathol. 2014;27 Suppl 2:4-536
27. O'Keefe M, Longacre TA, Kong CS, Folkins AK. Napsin A Has Utility in the Diagnosis of Clear Cell Carcinoma in the Ovary But May Be Less Valuable in the Endometrium [Abstract 1204]. Mod Pathol. 2015;28 Suppl 2:4-530.
28. Fadare O, Parkash V, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Rawish KR, Hecht JL, Desouki MM. Utility of α-methylacyl-coenzyme-A racemase (p504s) immunohistochemistry in distinguishing endometrial clear cell carcinomas from serous and endometrioid carcinomas. Hum Pathol. 2013;44:2814-21.

29. Masand RP, Malpica A, Deavers MT, Rao P, Ramalingam P. P504S (AMACRalpha-Methylacyl-coA Racemase): A Novel Marker of Clear Cell Carcinoma of the Female Genital Tract. Abstract 1203. Presented at the annual meeting of the United States and Canadian Academy of Pathology, Vancouver, BC, March 2012
30. Matias-Guiu X, Lerma E, Prat J. Clear cell tumors of the female genital tract. Semin Diagn Pathol. 1997;14:233-9.
31. Parra-Herran CE, Monte NM, Mutter GL. Endometrial intraepithelial neoplasia with secretory differentiation: diagnostic features and underlying mechanisms. Mod Pathol. 2013;26:868-73.
32. Tresserra F, Lopez-Yarto M, Grases PJ, Ubeda A, Pascual MA, Labastida R. Endometrial hyperplasia with secretory changes. Gynecol Oncol. 2003;88:386-93.
33. Gurda GT, Baras AS, Kurman RJ. Ki-67 index as an ancillary tool in the differential diagnosis of proliferative endometrial lesions with secretory change. Int J Gynecol Pathol. 2014;33:114-9.
34. Truskinovsky AM, Lifschitz-Mercer B, Czernobilsky B. Hyperplasia and carcinoma in secretory endometrium: a diagnostic challenge. Int J Gynecol Pathol. 2014;33:107-13.
35. McKenney JK, Longacre TA. Low-grade endometrial adenocarcinoma: a diagnostic algorithm for distinguishing atypical endometrial hyperplasia and other benign (and malignant) mimics. Adv Anat Pathol. 2009;16:1-22.
36. 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 Aug;31(8):1203-8.
37. Silverberg SG, Makowski EL, Roche WD. Endometrial carcinoma in women under 40 years of age. Comparison of cases in oral contraceptive users and nonusers. Cancer 1977;39:592–8.
38. Christopherson WM, Alberhasky RC, Connelly PJ. Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. Cancer 1982;49:1511–23.
39. Tobon H, Watkins GJ. Secretory adenocarcinoma of the endometrium. Int J Gynecol Pathol 1985;4:328–35.
40. Huntington RW Jr, Bullock WK. Yolk sac tumors of extragonadal origin. Cancer. 1970;25:1368-76
41. Ravishankar S, Malpica A, Ramalingam P, Euscher ED. Yolk Sac Tumor in Extragonadal Pelvic Sites: Still a Diagnostic Challenge. Am J Surg Pathol. 2017;41:1-11.
42. Damato S, Haldar K, McCluggage WG. Primary Endometrial Yolk Sac Tumor With Endodermal-Intestinal Differentiation Masquerading as Metastatic Colorectal Adenocarcinoma. Int J Gynecol Pathol. 2016 Jul;35(4):316-20.
43. McNamee T, Damato S, McCluggage WG. Yolk sac tumours of the female genital tract in older adults derive commonly from somatic epithelial neoplasms: somatically derived yolk sac tumours. Histopathology. 2016;69:739-751.
44. Przybycin CG, Yang B, Soslow, R. Primary endometrial yolk sac tumor (YST): Clinicopathologic and immunohistochemical characterization of a diagnostically problematic entity [Abstract]. Presented at the annual meeting of the United States and Canadian Academy of Pathology, March 2014.
45. Young RH, Hart WR. Metastatic intestinal carcinomas simulating primary ovarian clear cell carcinoma and secretory endometrioid carcinoma: a clinicopathologic and immunohistochemical study of five cases. Am J Surg Pathol. 1998;22:805-15.
46. Clement PB, Young RH. Endometrioid carcinoma of the uterine corpus: a review of its pathology with emphasis on recent advances and problematic aspects. Adv Anat Pathol. 2002;9:145-84
47. Zaino RJ, Kurman RJ. Squamous differentiation in carcinoma of the endometrium: a critical appraisal of adenoacanthoma and adenosquamous carcinoma. Semin Diagn Pathol. 1988;5:154-71.
48. O'Connell JT, Mutter GL, Cviko A, Nucci M, Quade BJ, Kozakewich HP, Neffen E, Sun D, Yang A, McKeon FD, Crum CP. Identification of a basal/reserve cell immunophenotype in benign and neoplastic endometrium: a study with the p53 homologue p63. Gynecol Oncol. 2001;80:30-6.
49. Stefansson IM, Salvesen HB, Akslen LA. Loss of p63 and cytokeratin 5/6 expression is associated with more aggressive tumors in endometrial carcinoma patients. Int J Cancer. 2006;118:1227-33.
50. Houghton O, Connolly LE, McCluggage WG. Morules in endometrioid proliferations of the uterus and ovary consistently express the intestinal transcription factor CDX2. Histopathology. 2008;53:156-65.
51. Chiarelli S, Buriticá C, Litta P, Ciani S, Guarch R, Nogales FF. An immunohistochemical study of morules in endometrioid lesions of the female genital tract: CD10 is a characteristic marker of morular metaplasia. Clin Cancer Res. 2006;12:4251-6.
52. Blanco LZ Jr, Heagley DE, Lee JC, Gown AM, Gattuso P, Rotmensch J, Guirguis A, Dewdney S, Bitterman P. Immunohistochemical characterization of squamous differentiation and morular metaplasia in uterine endometrioid adenocarcinoma. Int J Gynecol Pathol. 2013;32:283-92.
53. Yamani F, Fadare O. Arias-Stella Reaction in Progestin-Treated Endometrioid Adenocarcinoma: A Potential Diagnostic Pitfall. Int J Surg Pathol. 2016;24:330-1.
54. Fadare O. Expression of Napsin A is common in Arias-Stella reaction. Hum Pathol. 2016;54:202
55. Alvarez T, Miller E, Duska L, Oliva E. Molecular profile of grade 3 endometrioid endometrial carcinoma: is it a type I or type II endometrial carcinoma? Am J Surg Pathol. 2012;36:753-61.
56. Alkushi A, Köbel M, Kalloger SE, Gilks CB. High-grade endometrial carcinoma: serous and grade 3 endometrioid carcinomas have different immunophenotypes and outcomes. Int J Gynecol Pathol. 2010;29:343-50.
57. Ratner M, Schneiderman C. Metastasis to endometrium and skin from carcinoma of kidney: report of case and review of literature. J Urol 1948;61:389–92.

58. Stemmermann GN. Extrapelvic carcinoma metastatic to the uterus. Am J Obstet Gynecol 1961;82:1261–6.
59. Singh K, DiSilvestro PA, Lawrence WD, Quddus MR. An Isolated Metastasis From Clear Cell Renal Cell Carcinoma to the Uterus: A Case Report and Review of Literature. Int J Gynecol Pathol. 2016;35:419-22.
60. Rawish, KR, Osunkoya, AO, Gwin, K, Hanley, KZ, Hecht, JL, Jarboe, EA, Liang, SX, Parkash, V, Quick, CM, Zheng, W, Desouki, MM, Fadare O: Metastatic Clear Cell Renal Cell Carcinoma to the Gynecologic Tract: Clinicopathologic Analysis and Immunophenotypic Comparison with Mullerian Clear Cell Carcinomas [Abstract]. Presented at the United States and Canadian Academy of Pathology (USCAP) Annual Meeting, San Diego, CA, March 1 – 7. Mod Pathol 2014.
61. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. Eds, WHO Classification of Tumours of the Female Reproductive Organs. IARC: Lyon 2014
62. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6:93-108.
63. Gilks CB, Ionescu DN, Kalloger SE, Köbel M, Irving J, Clarke B, Santos J, Le N, Moravan V, Swenerton K; Cheryl Brown Ovarian Cancer Outcomes Unit of the British Columbia Cancer Agency. Tumor cell type can be reproducibly diagnosed and is of independent prognostic significance in patients with maximally debulked ovarian carcinoma. Hum Pathol. 2008;39:1239-51.
64. Köbel M, Kalloger SE, Baker PM, Ewanowich CA, Arseneau J, Zherebitskiy V, Abdulkarim S, Leung S, Duggan MA, Fontaine D, Parker R, Huntsman DG, Gilks CB. Diagnosis of ovarian carcinoma cell type is highly reproducible: a transcanadian study. Am J Surg Pathol. 2010;34:984-93
65. Köbel M, Bak J, Bertelsen BI, Carpen O, Grove A, Hansen ES, Levin Jakobsen AM, Lidang M, Måsbäck A, Tolf A, Gilks CB, Carlson JW. Ovarian carcinoma histotype determination is highly reproducible, and is improved through the use of immunohistochemistry. Histopathology. 2014;64:1004-13.
66. Han G, Gilks CB, Leung S, Ewanowich CA, Irving JA, Longacre TA, Soslow RA. Mixed ovarian epithelial carcinomas with clear cell and serous components are variants of high-grade serous carcinoma: an interobserver correlative and immunohistochemical study of 32 cases. Am J Surg Pathol. 2008;32:955-64.
67. DeLair D, Han G, Irving JA, Leung S, Ewanowich CA, Longacre TA, Gilks CB, Soslow RA. HNF-1beta in ovarian carcinomas with serous and clear cell change. Int J Gynecol Pathol. 2013;32:541–546
68. Mackenzie R, Talhouk A, Eshragh S, Lau S, Cheung D, Chow C, Le N, Cook LS, Wilkinson N, McDermott J, Singh N, Kommoss F, Pfisterer J, Huntsman DG, Köbel M, Kommoss S, Gilks CB, Anglesio MS. Morphologic and Molecular Characteristics of Mixed Epithelial Ovarian Cancers. Am J Surg Pathol. 2015;39:1548-57.
69. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol. 2013;37:874-81.
70. Fadare O, Parkash V, Dupont WD, Acs G, Atkins KA, Irving JA, Pirog EC, Quade BJ, Quddus MR, Rabban JT 3rd, Vang R, Hecht JL. The diagnosis of endometrial carcinomas with clear cells by gynecologic pathologists: an assessment of interobserver variability and associated morphologic features. Am J Surg Pathol. 2012;36:1107-18.