Endometrial Cancer Precursor Lesions: WHO is Better (?)

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Endometrial Cancer Precursor Lesions: Discussion Points

Although there is little doubt that there are some forms of altered endometrial glandular proliferations that, when present, pose an increased risk of adenocarcinoma, the histologic definition of these risk lesions and their relative risk is the subject of ongoing controversy. Despite the advances in molecular biology of endometrial neoplasia, our knowledge of endometrial carcinoma and its precursor lesions is meager compared to precancer lesions in the breast and colon, and unlike these latter two organ systems, the acquisition of new knowledge is beset by formidable methodologic problems (3):

1) The morphologic definition of the target event (adenocarcinoma, usually grade 1 adenocarcinoma) is ill defined, subject to poor interobserver agreement, and a matter of ongoing debate. We use myoinvasion as the target event in our definition of grade 1 endometrial adenocarcinoma (i.e., only those proliferations that have been observed to be associated with myometrial invasion with significant frequency are considered “adenocarcinoma” with other lesser degrees of glandular proliferation considered “atypical” or “borderline”) (9).

2) Even if one were to use myoinvasive adenocarcinoma as the target event, the morphologic definition of myoinvasion (particularly superficial myoinvasion and adenocarcinoma involving adenomyosis) is subject to poor interobserver reproducibility. Ideally, the definition of an endometrial precursor lesion would be geared toward identifying those lesions that pose a significant risk for progression to clinically significant adenocarcinoma - i.e., myoinvasive carcinoma – not (to borrow a phrase used to designate very low risk lesions in the prostate) the pathologist’s carcinoma.

3) Unlike other organ systems, the putative precursor lesions in the endometrium are anatomically unstable; they can be shed spontaneously, or they can be reversed by a change in the patient's hormonal milieu, whether through alterations in physiology or alterations produced iatrogenically.

4) The endometrial sampling procedure is essentially a screening tool – not all of the endometrium may be represented in any given sampling, regardless of the technique and even when it is, the presence of a myometrial lesion cannot be assessed. Most pathologists and surgeons assume the presence of cancer in the myometrium (myoinvasive cancer) is associated with cancer in the endometrium. Fortunately, this is often the case, but there are occasional cancers that invade without an appreciable exophytic component (much like some invasive colorectal cancers in patients with longstanding ulcerative colitis).

5) Another unique feature of endometrial glandular proliferations is the variety of altered cytoplasmic differentiation or metaplastic patterns that commonly occur in both benign, precursor and cancer lesions. Since some of these altered differentiation patterns exhibit slightly more cytologic atypia than that which is
associated with standard endometrioid differentiation, definitions of precursor lesions must take into account this variable cytologic appearance. For example, ciliated change typically contains rounder nuclei, often with small nucleoli, and some of the problems with earlier definitions of atypical hyperplasia failed to take this into account. (A similar problem presents itself in the breast with apocrine lesions.)

6) Given the absence of evidence-based and consensus-driven diagnostic criteria, there is a perception that existing criteria for the diagnosis of endometrial cancer and its precursor lesions suffer from such poor reproducibility, that the willingness of the surgeon and patient to retain the organ involved by any putative precancerous lesion to wait out its natural history is low, particularly in the usual age group in which these lesions develop.

7) The use of surrogate markers (such as PTEN in the proposed endometrial intraepithelial neoplasia scheme) to inform our morphologic definitions of precancer and cancer must meet minimum criteria required for the use of a surrogate marker in other organ systems: i.e., be sensitive and specific, reproducible, and subject to independent confirmation.

8) Current terminology and definitions for endometrial precursor lesions are imprecise, but the introduction of new terminology should be conducted with caution. For example, the concept of “intraepithelial” is at best imprecise in the endometrium, given the absence of a bona fide basement membrane (such as is seen in the cervix), and at worst erroneous, given the emerging recognition in other organ systems of apparent shared properties of some in situ and invasive cancers.

WHO Is Best?

The WHO criteria for endometrial cancer precursor lesions are based on the study by Kurman and colleagues in 1985 (7). In that study, the risk of progression to carcinoma was 23% for atypical endometrial hyperplasia, whereas it was only 2% for non-atypical hyperplasia. Although the target lesion in this study was “carcinoma” and not “myoinvasive adenocarcinoma,” we know from previous studies that the definition(s) used for carcinoma in that study are, with minor exceptions, a reasonable stand-in for myoinvasive grade 1 endometrial cancer (9).

The histologic criteria for complex atypical hyperplasia that were used in that study are well recognized and included a variety of cytologic and architectural features: nuclear enlargement, nuclear rounding, nucleoli, abnormal chromatin distribution (either dispersed or clumped), some degree of pleomorphism, loss of nuclear polarity, and a shift in the nuclear-to-cytoplasmic ratio in favor of the nuclei. The relative size of the nuclei was estimated by comparing them to the surrounding stromal cell nuclei or those of residual...
normal epithelial elements. Mitotic figures were almost always present in atypical hyperplasia and often numerous, but abnormal division figures were sparse or absent. In the study published by Kurman and associates, once a patient had atypical hyperplasia, no further insight into risk was provided by grading the degree of atypia; that is, varying degrees of cytologic atypia were not reflected in a greater or lesser risk of adenocarcinoma once it was determined that the endometrium was architecturally complex and the glands were lined by cytologically atypical cells (6). This is not unexpected, given the narrow range of atypia that is present in these lesions.

Subsequent reports using the Kurman criteria, provide additional evidence that approximately 20% to 30% of women with endometrial hyperplasia characterized by glands with marked architectural complexity and crowding, in addition to cytologic atypia, progress to a pattern that the investigators deemed morphologic adenocarcinoma (4). That is to say, not all precancers appear to progress to malignancy, either in the form of myoinvasion or clinical relapse, but a significant and diagnostic reproducible proportion do so despite the inherent difficulties in this diagnostically difficult range of endometrial glandular proliferations.

Although the World Health Organization, which is largely based on data from the Kurman et al study, proposes a four-tiered classification, in most workers’ experience, the vast majority of cytologically atypical lesions are architecturally complex and therefore, the degree of cytologic atypia, despite its inherent reproducibility problems, may well be the best discriminator for precancer in this range of glandular proliferation.

The degree of interobserver agreement for the diagnosis of “atypical hyperplasia” has been addressed by Kurman and coworkers (6). In that study, the only cytologic feature that was strongly associated with distinguishing hyperplasia (low risk for progression) from atypical hyperplasia (significant risk for progression) was the presence of nucleoli. The overall reproducibility for the diagnosis of “atypical hyperplasia” was moderate (kappa = 0.36 to 0.54) (6), while the overall reproducibility for the diagnoses of “hyperplasia” and “grade 1 carcinoma” were substantial. The interobserver reproducibility using the WHO criteria was more variable due to the use of 4 categories as opposed to 2, but was moderate overall and did not exceed that for the 2 category classification. Despite the utility of nucleoli in reproducibly distinguishing “hyperplasia” from “atypical hyperplasia” in that study, consensus diagnosis was achieved using a variety of pathways, not all of which entailed a conscious assessment for the presence of nucleoli (6). An experiential component combined with integration of multiple simultaneous evaluations appears to be inherent in the process of evaluating endometria for the presence of a risk lesion. Since the 2 tiered classification system of “hyperplasia” and “atypical hyperplasia” appears to perform as well as the 4 tiered WHO classification, the use of the 2 tiered system would appear to be preferable.

Can We Do Better?
To appropriately answer the question as to what is the best method of diagnosing precancer in the endometrium, one has to pose the question: to what end? For the purposes of generating a molecular-based understanding of endometrial carcinogenesis, a classification scheme based on molecular correlates is of obvious scientific and possibly, epidemiologic value. For the purposes of clinical decision making, any taxonomic scheme that is used to classify precancer in the endometrium should reflect what is known about cancer risk – i.e., myoinvasive, clinically significant cancer risk. Ideally, the two end-points are complementary, but experience has shown that this is often not the case and standard histologic criteria based on outcome remain the gold standard. In absence of a carefully defined and consensus-driven target lesion to assess outcome and hence, inform our diagnostic criteria for endometrial cancer and precancer, studies such as those recently published from the GOG that reported a dismally and unacceptably low level of pathologist reproducibility for atypical hyperplasia and low grade carcinoma will continue to plague our literature and our profession (15-17).

Given the formidable methodologic problems itemized above, one nihilistic view is that this is the best we can do. Another, perhaps more optimistic view is to search for molecular correlates of cancer and precancer to inform and improve on our standard histologic assessment. However, before we throw up our hands in defeat or rush to blindly embrace the molecules, it is important to remember that it may not always be necessary to render a finely tuned definitive diagnosis for this problematic set of lesions. In any given patient, it may be enough to give a best estimate of risk so that the treating physician and patient can make an informed decision to pursue a trial of hormonal therapy or proceed to a more definitive diagnostic (and therapeutic) procedure. In order to develop a more effective, real-world patient management program, further attempts to develop refined, evidence-based, and consensus-driven diagnostic criteria for these endometrial risk lesions should address these methodologic problems in well-designed, systematic, large-scale and independently confirmed studies.

**Selected References**


