Mixed Epithelial Carcinoma of the Endometrium: Recommendations for Diagnosis from the ISGyP Endometrial Carcinoma Project

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Introduction

The 2014 edition of the World Health Organization (WHO) Classification of Tumors of the Female Reproductive Organs recognizes mixed carcinoma (also called mixed cell adenocarcinoma by WHO) as a specific histologic category of epithelial endometrial cancer.(1) The 2014 WHO defines it as a tumor composed of ***"two or more different histological types of endometrial carcinoma, at least one of which is of the type II category.***" The term "type II" category refers to non-endometrioid, non-mucinous types (e.g. serous carcinoma, clear cell carcinoma, carcinosarcoma). The rationale for recognizing this category stems largely from the adverse behavior of tumors that contain as little as 5% of a component of serous carcinoma admixed with endometrioid adenocarcinoma, with the implication that the type II tumor component should drive patient management. The International Society of Gynecologic Pathologists (ISGyP) Endometrial Carcinoma Project has reviewed this definition and identified areas that merit clarification and areas that remain controversial. This lecture will address practical recommendations for the diagnosis of mixed epithelial carcinoma of the endometrium and review the key entities in the differential diagnosis.

Clinical Significance

The literature on mixed epithelial carcinoma of the endometrium is composed of three kinds of studies: 1.) studies of endometrial serous carcinoma in which some of the cases are pure serous carcinoma and some are mixed with endometrioid adenocarcinoma; 2.) studies of endometrial clear cell carcinoma in which some cases are pure and some are mixed with other cancer types; 3.) studies specifically of mixed endometrial cancers. Most of the literature relates to the first kind whereas the studies of the third kind are focused on molecular characteristics rather than behavior. There are limitations to the literature that merit acknowledgement: First, morphologic and immunohistochemical criteria for endometrioid, serous and clear cell carcinoma have evolved over the span of time (1990's to current day) during which these studies were conducted. Second, there is variability across studies in the minimum amount (e.g. 5%, 10%, 20%) of the secondary component of type II tumor required to qualify as mixed carcinoma. Third, new types of tumors have been recognized recently (e.g. dedifferentiated endometrial carcinoma) that may have been classified as mixed carcinomas in earlier studies. These, and other study design limitations, make it challenging to directly compare some of the earlier studies to more contemporary ones.

Serous carcinoma mixed with endometrioid adenocarcinoma

Historically, some studies suggest that between 20% and 50% of endometrial serous carcinomas are mixed with endometrioid adenocarcinoma, though that estimate may be much lower using contemporary morphologic and immunohistochemical criteria. At least 7 studies(2-8) using multivariate analysis showed that there is no difference in survival between pure or mixed serous carcinoma. In slight contrast, at least 3 studies(9-11) using multivariate analysis showed that survival of mixed serous carcinoma was intermediate between that of pure serous carcinoma and pure endometrioid adenocarcinoma. The minimal amount of serous carcinoma that carries clinical relevance is less clear but a few studies demonstrate that as little as 5% to 10% can be associated with the same recurrence and survival as pure serous carcinoma. (12) (13) There is no literature on the reproducibility of quantifying the percent of a specific tumor type in an overall tumor and so there is no evidence to justify excluding serous carcinomas that constitute <5% of an overall tumor if the diagnosis can be made confidently.

Clear cell carcinoma mixed with endometrioid adenocarcinoma

Historically, studies suggest that between 10% and 50% of endometrial clear cell carcinomas are mixed with endometrioid adenocarcinoma, though that estimate may be much lower using contemporary morphologic and immunohistochemical criteria. Compounding the accuracy of this estimate is the problem of interobserver variability in the diagnosis of endometrial cancers with clear cells, some of which may truly be clear cell carcinoma whereas some may represent variations of endometrioid adenocarcinoma or serous carcinoma.(14) One study(15) using multivariate analysis demonstrated that the presence of at least 10% clear cell carcinoma in otherwise endometrioid adenocarcinoma was associated with the same survival as pure clear cell carcinoma. The remainder of the literature is limited by sample size and study design.

Pathogenesis

Several models for the pathogenesis of mixed carcinomas have been proposed.(16) The collision theory proposes that the two tumor types arose from independent pathways. In contrast, the morphologic mimicry theory proposes that mixed

carcinomas represent a single tumor type that focally developed a component of divergent morphology that mimics a second tumor type. Alternatively a type II tumor could arise from a type I tumor that acquires a secondary mutation; for example a p53 mutation that occurs in an endometrioid adenocarcinoma could give rise to a component of serous carcinoma. In 2015, Kobel et al(16) reported the molecular profiles of 11 mixed serous and endometrioid adenocarcinomas, 5 mixed clear cell and endometrioid adenocarcinoma and 2 mixed clear cell and serous carcinomas. In most of the cases, the different morphologic components were clonally related and shared similar molecular alterations, suggesting that most mixed carcinomas represent a single tumor with varied morphology and that true collision tumors are rare.

ISGyP Recommendations for Diagnosis of Mixed Carcinoma of the Endometrium

1. Endometrioid adenocarcinomas that contain a spatially distinct component of serous carcinoma or clear cell carcinoma should be reported with a diagnosis that lists each type of tumor, the percent of the overall tumor composed of each type, and the grade of the endometrioid component. The WHO term “mixed endometrial carcinoma” can also be used parenthetically but should not be used alone in lieu of reporting each tumor type, percent composition, and grade.

2. Any amount of serous carcinoma or clear cell carcinoma that can be confidently recognized on routine H&E staining in an otherwise endometrioid adenocarcinoma should be reported. A second observer and/or immunohistochemistry is advised to confirm the presence of a component of serous carcinoma (aberrant p53 and p16) and/ or clear cell carcinoma (positive Napsin A).

3. The overall tumor grade of a mixed carcinoma is grade 3 by definition due to the presence of the component of serous carcinoma or clear cell carcinoma. The overall grade is not dependent on the percent of serous carcinoma or clear cell carcinoma that is present.

Using these criteria, mixed carcinoma should be an uncommon diagnosis. This category should not be used for certain special tumor types or morphologic variants of endometrioid adenocarcinoma that mimic type II tumors(17, 18):

- Dedifferentiated endometrial carcinoma(19, 20) and carcinosarcoma should not be reported as a mixed endometrial carcinoma but as their own types, using 2014 WHO criteria.
- Papillary variants of endometrioid adenocarcinoma should be distinguished from serous carcinoma and should not be reported as mixed endometrioid and serous carcinoma.
- Clear cell change in endometrioid adenocarcinoma should be distinguished from clear cell carcinoma and should not be reported as mixed endometrioid and clear cell carcinoma.
- Glandular variants of serous carcinoma should be distinguished from endometrioid adenocarcinoma and should not be reported as mixed endometrioid and serous carcinoma.
- The corded and hyalinized type of endometrioid adenocarcinoma (21) should be distinguished from carcinosarcoma and reported as endometrioid adenocarcinoma and not as mixed carcinoma.
- Tumors that are difficult to classify because of overlapping morphologic and immunohistologic features of serous, clear cell and endometrioid differentiation should not be reported as mixed endometrial carcinoma. Such tumors have been categorized as exhibiting ambiguous morphology(22), which is a separate issue from tumors with two spatially distinct types of cancer.
- The differential diagnosis of carcinosarcoma should be considered in cases with a mixed glandular component since this may be a feature of carcinosarcomas.

Unresolved Issues

The minimum amount of a component of a type II (non-endometrioid, non-mucinous) cancer that portends a potentially aggressive behavior in a tumour which otherwise comprises a low grade endometrioid adenocarcinoma remains to be well-defined. This can only be established by multi-institutional studies of well sampled cases using clearly defined morphologic and immunohistochemical criteria.

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