Modern Pathology (2011) 24, 1281–1283

Letters to the Editor

Letter to the editor regarding 'Roh MH, Lassin Y, Miron A *et al*. High-grade fimbrial-ovarian carcinomas are unified by p53, PTEN and PAX2 expression'

Modern Pathology (2011) **24,** 1281–1282; doi:10.1038/modpathol.2011.94

To the Editor: We read with interest the recent paper by Roh *et al* entitled 'High-grade fimbrial-ovarian carcinomas are unified by p53, PTEN and PAX2 expression'.[1] We note that they continue to make a distinction between high-grade serous, high-grade endometrioid and mixed serous and endometrioid carcinoma in their study on high-grade fimbrial-ovarian carcinomas.[1] The distinction between high-grade serous and high-grade endometrioid carcinoma of the ovary has been poorly reproducible in the past.[2–5] Global gene expression profiling has highlighted the molecular similarities between tumors diagnosed as high-grade serous carcinoma and high-grade endometrioid carcinoma,[6,7] and WT1 immunostaining profiles of these tumor types are identical (as shown by Roh *et al*[1]).[8,9] This has led to increasing recognition that most of those tumors diagnosed as high-grade endometrioid carcinomas in the past are indistinguishable from high-grade serous carcinomas,[10–12] completely distinct from the endometrioid carcinomas that meet the WHO criterion, ie, 'closely resemble the common variant of endometrioid carcinoma of the uterine corpus',[13] and are tumors that are typically low-grade and are frequently associated with endometriosis. This simple change in practice results in a highly reproducible classification of ovarian carcinoma based on tumor cell type,[14] with a classification system that reflects the underlying differences in molecular abnormalities, outcomes and response to treatment (reviewed in Gilks and Prat[12]). It is also of clinical importance as only the high-grade serous carcinomas are significantly associated with germline BRCA mutations,[15] which has implications for both referral to genetic counseling and BRCA testing, and for therapy, now that PARP inhibitors have been shown to have activity against high-grade serous carcinomas even in the absence of BRCA germline mutations.[16] Diagnosis of high-grade ovarian/tubal/peritoneal carcinomas as endometrioid, based on an undefined and irreproducible component showing glandular differentiation, is a step backwards, going against the dramatic advances in histopathological assessment of ovarian carcinoma, which are now increasingly reflected in ovarian cancer subtype-specific management. The latter is likely to increase in the future with ongoing trials investigating the efficacy of alternative chemotherapeutic agents in different morphological subtypes of ovarian carcinoma. We do recognize that occasional high-grade endometrioid carcinomas arise in the ovary, but we feel these are uncommon, often associated with squamous elements and endometriosis, and are WT1 negative in most cases.

Roh *et al* do make the interesting observation that the tumors they diagnose as high-grade endometrioid carcinoma are less likely to be associated with tubal intraepithelial carcinoma (a difference that does not reach statistical significance), and more likely to be associated with a dominant ovarian mass, but that alone, given the compelling evidence that these tumors are molecularly and immunohistochemically indistinguishable from high-grade serous carcinomas, is not a sufficient basis to regard them as distinct tumor subtypes. It is possible, for example, that the glandular architecture of the tumors diagnosed as high-grade endometrioid carcinoma is a result of their intra-ovarian growth, rather than a cause (just as papillary growth is more common on the surface of endometrial carcinomas, compared with the myoinvasive component). The potential harm in continuing to use the diagnosis 'endometrioid' for these carcinomas is significant, as it undercuts the recent advances in the diagnosis of ovarian carcinoma subtype, which in turn opens the door to subtype-specific management. If ovarian cancer subtype diagnosis is irreproducible it creates an impasse, as attempts at subtype-specific management are impossible if pathologists cannot agree on the subtype.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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Response to Gilks *et al*

Modern Pathology (2011) **24,** 1282–1283; doi:10.1038/modpathol.2011.79

To the Editor: The crux of this letter is a disagreement with the term 'high-grade endometrioid carcinoma'. First, the authors point out that the diagnosis is not easily reproduced between pathologists. Second, they state that the molecular data indicate very little difference between high-grade endometrioid and high-grade serous carcinomas.[1] Third, they perceive that continued use of the term 'high-grade endometrioid' will create confusion that will be detrimental to patient care. Fourth, they imply that the differences in the frequencies of two parameters—tubal intraepithelial carcinoma and dominant ovarian mass—in cases of high-grade serous and endometrioid carcinomas are insufficient reason to separate them.

We agree with the first two statements and anyone who properly reads the paper by Roh *et al*[2] should arrive at the same conclusion. Each case of high-grade muellerian carcinoma analyzed in our study was re-reviewed and re-classified into three categories in recognition of the problem of subclassifying these tumors. It should be obvious that we performed this study to determine whether differences existed between the histological groups. In fact, the summary statement in the abstract applies the term 'high-grade muellerian carcinoma' to this group of tumors. Using this term in practice addresses the third argument by making it clear to the oncologist that the tumor is not a low-grade endometrioid adenocarcinoma. Because these high-grade malignancies are typically high-stage when diagnosed, patients will not be harmed by this terminology.

But women who must deal with this disease, either directly or indirectly, and the field of ovarian cancer research in general, would be ill served by premature efforts to increase reproducibility by ignoring histological variation. In our study, we found only one tubal intraepithelial carcinoma in 12 cases of high-grade endometrioid carcinoma, which