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Short Communication

Endocervical Adenocarcinoma: A Paradigm Shift in Classification

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Cervical cancer is the fourth most common malignancy in females worldwide [1]. Amongst others, squamous cell carcinoma is the most prevalent histological subtype, which is very often associated with human papillomavirus (HPV) infection. On the other hand, endocervical adenocarcinomas (ECAs) comprise merely 25% of all primary cervical carcinomas [2]. Majority of the endocervical adenocarcinomas are HPV-related and harbor a strong association with high-risk genotypes of HPV. However, approximately 5.5 - 11% of all ECAs are reported to be HPV-negative and are, therefore, regarded as non-HPV-associated ECA. These non-HPV-driven subtypes of endocervical adenocarcinoma have distinct clinic-pathologic features and confer a poor prognosis [3]. Therefore, efforts were made to improve the classification of ECA and to establish clinically relevant and reproducible criteria for classifying cervical glandular malignancies.

The 2014 World Health Organization (WHO) classification of cervical tumors categorizes ECAs based on morphologic characteristics (predominantly cytoplasmic features). This system entirely bypasses the current evidence for different pathogenetic mechanisms in various subtypes of ECAs and divides them based on traditional histomorphology into two broad categories, namely mucinous and non-mucinous neoplasm [2,3]. The International Endocervical Adenocarcinoma Criteria and Classification (IECC) proposed in 2018, is a multinational collaborative comprising of 409 cases of ECA from 7 institutions worldwide. This study aimed to differentiate HPV-associated adenocarcinoma (HPVA) and non-HPV-associated adenocarcinoma (NHPVA) by morphology alone. The defining criteria for HPVA included apical mitotic figures and apoptotic bodies appreciable at scanning magnification (x20 or x40). If these were not easily recognized and were visible only on high power (x400) or not visible at all, that indicated a lesion unrelated to HPV infection and was tentatively regarded as NHPVA. Further, these lesions were sub-classified based on conventional criteria established by WHO. Immunohistochemistry (IHC) for p16, p53, vimentin, and progesterone receptor (PR) as well as ribonucleic acid in-situ hybridization (RISH) for HPV were performed to validate the IECC diagnoses. This classification scheme exhibited high concordance with IHC and RISH results, while only 3% of cases were morphologically categorized as NHPVA and were also positive for HPV RISH. Additionally, important demographic and clinical differences between HPV-associated adenocarcinoma and non-HPV-associated adenocarcinomas were highlighted by the study. NHPVA were larger, developed in older patients, and were diagnosed at an advanced FIGO stage than HPVA [4]. As opposed to the former, lymphovascular invasion, lymph node metastasis, and Silva C pattern were uncommon in HPVA. They responded better to adjuvant therapy and, hence had enhanced overall survival, disease-free survival, and progression-free survival [5].

Recent studies authored by Hodgson., *et al.* [6] and Ren., *et al.* [7] have affirmed that the IECC grants a more reproducible system to sub-classify ECAs as compared to 2014 WHO classification with an improved interobserver agreement and excellent correlation with HPV status. Thus, it cannot be emphasized enough that IECC is superior to the previous WHO 2014 classification as it incorporates etiopathogenic factors, histology, and molecular characteristics in classifying ECAs. It is worthwhile to mention that the 5th edition

of the WHO classification of female genital tumors adheres to the recommendations of IECC and categorizes ECAs based on the HPV status.

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