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EDITORIAL:
MULTIMODAL STRATEGY OF HPV DETECTION

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The last formal review on the carcinogenicity of human papillomavirus (HPV) conducted in 2009 by the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence demonstrating the carcinogenicity of HPV16 in the oropharynx and possibly in the oral cavity[1].

IARC Monograph Working Group on Biological Agents classified 12 different high risk (HR)-HPV types as carcinogenic to humans: types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV16 and HPV18 are the types most frequently found in cervical cancers worldwide. It is now well demonstrated that HR HPV types are also involved in a subset of other genital cancers, such as vulvar, vaginal, anal, and penile cancers, as well as head and neck cancers (HNC). Approximately 25% of oropharyngeal carcinomas worldwide are linked to HR HPV infections, while the role of these viruses in HNC, such as cancers of the oral cavity, larynx, and hypopharynx, appears to be considerably less significant. Among the HR HPV types, HPV16 is responsible for the majority (86–95%) of HPV-positive oropharyngeal carcinomas[1,2]. In patients with oropharyngeal carcinoma, the detection of HPV is emerging as a valid biomarker for discerning the presence and progress of disease encompassing all aspects of patient care[3,4]. HPV testing is increasingly used for more refined tumor staging.

Detection strategies vary not just in design, but in their detection targets. These targets have included HPV DNA, HPV RNA, viral oncoproteins, cellular proteins and HPV-specific serum antibodies. None of the single methods offers optimal sensitivity and specificity levels. Therefore, stepwise algorithms combining different HPV tests should be designed. Gloghini et al in this issue of the Journal propose an original algorithm as a strategy to compensate for the limitations of individual tests[5]. Multimodality detection strategies look to utilize the strength of individual assays in combination to optimize the overall reliability of HPV detection. The algorithm proposed uses multiple methods of HPV detection beginning with p16 immunohistochemical staining and HR-HPV DNA in situ hybridization method. E6/E7 mRNA PCR-based methods (either real time RT-PCR or ISH) are used in p16 positive/HR-HPV DNA negative carcinomas to confirm the presence of HPV. According to Gloghini and co-workers this multimodal strategy offsets the limitations of individual tests.

The limitations of individual tests rely on technical considerations. The main problem with PCR-based methods is the interpretation of results. Indeed, these methods are extremely sensitive, but analytic (laboratory) sensitivity should be distinguished from clinical relevance. With PCR-based methods it is not possible to determine if viral sequences arise from the population of cancer cells, or from the surrounding non-neoplastic tissue[6]. The final goal of any HPV detection strategy, in oropharyngeal carcinomas, lies in its ability to recognize the presence of HPV and above all its implications in oncogenesis. E6 and E7 viral oncogenes, by inhibiting TP53 and pRb

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respectively, play a key role to the development of cancer. E6/E7 messenger RNA (mRNA) is the current gold standard for detecting clinically relevant HPV. However, the method requires RNA extraction and is inadequate for routine screening. Importantly, a novel ISH technique called RNAscope™ HPV test (Advanced Cell Diagnosis, Hayward, CA) detects E6/E7 mRNA from HR-HPVs. This assay may solve current clinical controversies about HR-HPV involvement as it confirms, simultaneously, the presence of integrated and transcriptionally-active virus in FFPE samples[7]. However, limited data are available for this novel technique.

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