Introduction: Human Papillomavirus in Head and Neck Cancer: An Update for 2012 with a Focus on Controversial Topics

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Abstract Human papillomavirus has emerged as a major pathogen, capable of causing cancer at many different sites. In the head and neck, human papillomavirus is associated with many squamous cell carcinomas and is particularly important in the oropharynx. This is a fast moving topic with many important epidemiological, biological, pathological, and clinical features that are often confusing and misunderstood. This article introduces a series of timely reviews and editorials on this important subject in head and neck oncology.

Keywords Human papillomavirus · p16 immunohistochemistry · Squamous cell carcinoma · Oropharynx · Survival · Head and neck

The search for novel biomarkers to predict prognosis, guide treatment, or to serve as potential therapeutic targets has been ongoing in head and neck cancer research for the past 50 plus years. However, few such biomarkers have emerged. It is against this backdrop that we have seen one of the most dramatic advances in our understanding of head and neck squamous cell carcinoma (SCC)—the discovery of biologically-active human papillomavirus (HPV) in oropharyngeal SCC [1]. Indeed, as our understanding of the

biology of these virally-driven tumors has grown in the last several years, we have come to realize that there has been a growing epidemic of these cancers dating back at least to the 1970s [2]. We have also recognized the power of HPV as a prognostic biomarker [3]. HPV in oropharyngeal SCC has been shown to provide the widest risk stratification for survival of any head and neck biomarker ever discovered, and it is clear that in the near future, it will have important therapeutic implications as well [4, 5].

The role of HPV in head and neck SCC is a rapidly advancing area of medicine with large numbers of studies and review articles published each year. Thus, it becomes very difficult to keep up with the data. In addition, there are many controversial areas where quality data are lacking or, more commonly, where there is a wealth of data but differing opinions on what it says about tumor biology, clinical behavior, patient prognosis, or treatment.

With this particular collection of review and editorial articles by a diverse, international collection of experts in the field, we at *Head and Neck Pathology* hope not only to provide a “one-stop shopping” timely update on current knowledge but, moreover, to clarify many of the emerging concepts. Also, by grouping articles presenting differing viewpoints on a few major controversial subjects, we hope to help readers better understand these controversies and also the thinking behind these viewpoints. Since HPV is clearly most biologically relevant and clinically important in oropharyngeal SCC, the articles will focus primarily on this anatomic subsite. Some articles, however, will address HPV in non-oropharyngeal SCC and in other head and neck cancers.

Dr. Stina Syrjänen first provides a thorough review of HPV biology and specifically addresses carcinogenesis in head and neck tumors. Dr. Anil Chaturvedi then gives a timely update on the epidemiological and clinical aspects

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of HPV-related oropharyngeal SCC, and Dr. Patricia Hudgins discusses the many radiologic imaging features of HPV-related SCC and the various imaging modalities used to study them.

As mentioned, several controversies in this area of oncology are addressed here by presenting opposing viewpoints on them. The first involves basic histologic morphology of routine HPV-related oropharyngeal SCC. Drs. William Westra and Rebecca Chernock present perspectives on tumor morphology of routine oropharyngeal SCC in the HPV era, what terminology to use for such tumors and what to avoid, and differing perspectives on how and what to report in the pathologic examination of the specimens. There are many specific histologic variants of head and neck SCC that occur in the oropharynx and elsewhere. Much is being learned about their biology and, in particular, about HPV in them. Dr. Samir El-Mofty presents an update on five of the main variants and what HPV in these tumors appears to mean clinically.

The second controversial area involves identification of oropharyngeal SCC patients that have a favorable prognosis due to HPV. Given the myriad HPV-specific tests available, as well as surrogate markers such as p16 immunohistochemistry, there is significant disagreement as to how to provide risk stratification for patients in routine clinical practice. Dr. Aldo Venuti first discusses the myriad HPV detection methods, the surrogate marker p16, and then many other promising tests, such as plasma and saliva HPV detection, and also gene expression profiling and microarrays. To address how these could or should be applied in routine practice, I provide an analysis of p16 immunohistochemistry as a standalone test for patient risk stratification in oropharyngeal SCC, while Dr. Max Robinson and colleagues present the viewpoint that HPV-specific testing is requisite for all patients with oropharyngeal SCC.

The third and most obvious controversial area in HPV-related head and neck SCC involves treatment. Dr. Jennifer Grandis presents the viewpoint that primary radiation and systemic therapies are the optimal approach to treating most patients with oropharyngeal SCC. Dr. Eric Genden then elaborates on why many think that, in the era of transoral robotic and laser surgery, primary surgical management followed by the appropriate postoperative therapies (or obviating the need for it in some cases) is optimal.

Finally, there is a great deal of emerging knowledge about HPV and what its prevalence and role are in non-oropharyngeal head and neck cancers. Dr. Margaret Brandwein-Gensler provides the most up to date information by a focused review of the literature, specifically addressing oral cavity, laryngeal, hypopharyngeal, and sinonasal SCC and some new data in salivary gland carcinomas. Dr. Amanda Psyrri rounds out the issue by providing a perspective on future directions, including optimizing and/or de-escalating treatments for patients with HPV-related SCC, the potential of HPV-targeted therapies, and also a discussion of vaccination, both for treatment and prevention.

Clearly, the identification of transcriptionally-active (and clinically relevant) HPV in oropharyngeal SCC has been a huge advance in head and neck oncology. It has changed the direction of treatment and research in this field, introducing many new and very important questions. We hope that this collection of articles will provide our readership with a fundamental knowledge base that can guide clinical practice and also help investigators to study the virus to further elucidate its role in head and neck cancer.

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