Throat Cancer and Human Papillomavirus (HPV) Infection
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The term throat cancer refers to malignancies of the pharynx and larynx. The vast majority of these are squamous cell carcinomas (SCC). Traditional risk factors for throat cancer include tobacco use and alcohol consumption. However, in the oropharynx, particularly the tonsil, human papillomavirus (HPV) infection has emerged as a prominent risk factor. HPV is found in 45% to 95% of oropharyngeal SCC. Unlike tobacco-related throat cancer, which is decreasing in incidence with declining rates of tobacco use, HPV-related oropharyngeal SCC shows increasing incidence in several Western countries.

The association between oropharyngeal SCC and HPV infection is now well established. HPV subtypes are classified as high- or low-risk based on their malignant potential. Only high-risk HPV subtypes (including 16, 18, 31, 33, and 35) have been associated with oropharyngeal SCC of which HPV 16 is the most common subtype identified in HPV-positive cancers. High-risk HPV E7 protein binds to and degrades the retinoblastoma protein (pRb), which results in upregulation of the p16 protein. HPV-positive tumors frequently show high expression of p16, thus detection of the p16 protein by immunohistochemistry is considered a useful surrogate marker for HPV-positivity.

HPV-positive oropharyngeal SCC represents a distinct subset of head and neck SCC. HPV-positive cancers, especially tonsillar cancers, usually present at a younger age, and often without a prior history of tobacco and alcohol use. It appears, however, that HPV-associated oropharyngeal SCC is, in some ways, a sexually transmitted disease: factors such as number of sexual partners (including oral sex partners), prior history of genital warts, and HIV infection confer a higher risk of tonsillar and base-of-tongue cancers.

Despite smaller primary tumor sizes at presentation, HPV-positive cancers often present with large, cystic, nodal involvement. These lateral cervical metastatic masses may mimic branchial cleft cysts, especially in younger patients. Histologically, HPV-positive tumors are typically nonkeratinizing, and ‘basaloid’ in appearance, in contrast to the keratinizing appearance of HPV-negative SCC.

Overall, however, HPV-positive oropharyngeal SCC has a better prognosis than HPV-negative cancers, regardless of lymph node involvement, age, gender, clinical stage, tumor differentiation, or treatment strategy. Studies show an 80% to 95% two- to three-year overall survival rate for patients with HPV-positive SCC, compared to a 57% to 62% rate for those with HPV-negative cancers. The pathogenetic mechanisms underlying the association between HPV positivity and improved outcome are not clearly understood and may involve a combination of patient- and tumor-related factors. HPV-positive tumors have significantly fewer chromosomal abnormalities than HPV-negative cancers.
Oropharyngeal SCC is usually treated by surgical resection and adjuvant chemoradiotherapy. Transoral robotic surgery (TORS), an emerging robotic-assisted technology, offers disease control in both HPV-negative and HPV-positive patients with oropharyngeal SCC when followed by appropriate adjuvant therapy. The clinical benefits of TORS include avoidance or dose reduction of adjuvant chemoradiotherapy and improved swallow function and cosmetic outcome. Randomized controlled trials are needed to determine the appropriate role of TORS in clinical management.

The clinical significance of HPV infection in laryngeal SCC is unclear. Meta-analysis suggests that up to 25% of laryngeal SCC contains HPV infection and, as in oropharyngeal SCC, HPV 16 is the most commonly identified subtype.

In summary, HPV-related oropharyngeal SCC represents a distinct clinicopathologic subtype of head and neck SCC. HPV positivity in oropharyngeal SCC confers a better prognosis than HPV negativity, and HPV status is a robust prognostic indicator for overall survival, treatment response, and tumor control. HPV infection also occurs in laryngeal SCC, but the clinical relevance thereof requires further investigation.

References


