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Recent advances in managing human papillomavirus-positive oropharyngeal tumors

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Abstract

Human papillomavirus (HPV) is detected in a subset of patients with head and neck squamous cell carcinoma, most frequently in tumors in the Waldeyer's ring (palatine tonsil and base of tongue). Several studies suggest that patients with HPV-positive tumors have better survival with either concurrent chemoradiation therapy or surgery followed by radiation compared with HPV-negative patients. However, some possible confounding clinicopathologic variables may challenge the validity of this statement, for example, some authors used the TNM (tumor, node, metastasis) grouping stage while others used the primary tumor (T stage), and other studies have demonstrated that tumors with advanced T stage were less likely to be infected with HPV. A large clinical trial with stratification of patients according to all known tumor prognostic factors is crucial to solve the question.

Introduction and context

It has been well established that alcohol use or cigarette smoking or both are the most significant risk factors for the development of head and neck squamous cell carcinomas (HNSCCs). However, nearly every head and neck oncologist has come across patients, most of them young, with little or no tobacco or alcohol consumption (up to 20% in some cases) [1].

Sturgis and Cinciripini [2] demonstrated decreasing incidence rates for tobacco-associated oral, pharyngeal, and laryngeal cancers since the mid-1980s, and these rates trailed the declines in smoking prevalence by 10-15 years. On the other hand, oropharyngeal cancer is not demonstrating a similar decline [3]. Shiboski *et al.* [4] found a dramatic rise in the incidence rates of oropharyngeal cancer in adults younger than 45 years of age in the US (2% per year for base-of-tongue cancer and 4% per year for tonsil cancer). As far back as 1982, the presence of human papillomavirus (HPV) antigens in 36% of pathologic specimens of laryngeal cancers was demonstrated [5]. Since then, several hundred papers on this topic have been published. We made a query on PubMed using the key words 'HPV, head and neck cancer' and found 1410 papers.

Recent advances

HPV genomic DNA was detected in 26% of all HNSCCs [6], whereas approximately 50% of oropharyngeal cancers contained the HPV genome [7]. By contrast, in a multinational study, only 18% of oropharyngeal tumors were HPV^+ [8], indicating that this proportion varies with geography and sexual behavior (history of performing oral sex and oral-anal contact) [9]. Some studies found that patients who had sexual intercourse at an early age and more than six oral sexual partners in their lifetime had a fivefold risk of having HPV in their tumor compared with patients with no oral sexual partners [10,11]. Also, a significant racial difference in HPV positivity was found in a clinical trial of induction chemotherapy followed by concurrent chemoradiation therapy between white patients (35%) and black patients (4%) [12].

Several studies demonstrated an improved prognosis for patients with HPV^+ tumors versus patients with HPV^- tumors with (chemo)radiation treatment [7,13,14]. Other studies found the same results in both patients treated with radiation or surgery and radiation [15-18]. Haraf *et al*. [19], investigating the correlation between HPV infection and p53 mutation in HNSCCs, found that patients with p53 mutations had a history of heavier smoking in comparison with patients with HPV infection, who conversely had a more advanced stage at diagnosis. In a paper from our institution [20], we analyzed a homogenous group of surgically treated oropharyngeal cancers with or without postoperative radiotherapy according to commonly accepted pathologic risk factors. Patients were divided into three groups according to HPV, TP53 (tumor protein p53), and p16 status. Patients harboring high-risk HPV showed a significant improvement in terms of survival and occurrence of relapse and a lower incidence of smoking-related second primary tumors, independently of tumor stage and delivered treatment (surgery alone or surgery and postoperative radiotherapy), thus confirming that HPV^+ tumors represent a distinct disease among oropharyngeal cancers. In contrast, p53 mutation and p16 status seemed to lack prognostic significance in the absence of HPV infection. Similar results are reported by Weinberger *et al*. [21].

Begum *et al*. [22] detected HPV-16 in 22 of 68 (32%) lymph node metastases in patients with HNSCC and found that all HPV-16^+ lymph nodes were metastases from the oropharynx. Goldenberg *et al*. [23] found a correlation between patients with cystic lymph node metastases and the presence of HPV DNA. Almost all of these patients had a tumor in the palatine or lingual tonsil.

Implications for clinical practice

The quoted retrospective analyses must be interpreted with caution because of possible confounding data. For example, Schwartz *et al*. [17] analyzed HPV infection and survival in oral cancers, but 31.5% of their patients had an oropharyngeal tumor (tonsil and base of the tongue). Nevertheless, the association between HPV status and prognosis seems to be indisputable, with a better disease-specific survival for patients with HPV^+ oropharyngeal cancers in comparison with HPV^- patients, whereas disease-specific survival was similar for HPV^+ or HPV^- patients with nonoropharyngeal cancer [24]. Some authors even demonstrated a worse prognosis for HPV^+ patients with laryngeal and hypopharyngeal carcinomas in comparison with HPV^- patients [25]. Hence, the matter seems to be restricted to oropharyngeal cancer, and the diagnosis of HPV positivity should enter as a routine test for these patients. The most clinically useful test, *in situ* hybridization, is available in only a few centers which is unfortunate, even if p16 immunohistochemistry may serve as a reasonable surrogate [7].

Another possible bias in the interpretation of the results of some studies is due to the staging of the presented patients, as some authors used the AJCC-UICC (American Joint Cancer Committee/Union Internationale Contre le Cancer) stage grouping [12,15,18,20,24,26]. It is well known that in stage III there are T1-N1 and T3-N0 tumors, and in stage IVA there are T1-N2 and T4a-N0, and these are clearly different tumors. Looking to those papers reporting T stage, we may realize that although overall TNM (tumor, node, metastasis) stage does not differ by HPV status, HPV^+ tumors are more likely than HPV^- tumors to have a lower T stage [16,27], whereas advanced T stage is a significant risk factor for recurrence and death, independently of HPV status [14]. Some historic papers on results of radiation therapy for oropharyngeal tumors demonstrated that vegetating tumors (T1-T2) are more curable than infiltrating tumors (T4) [28,29]. Shonka *et al*. [30] demonstrated that patients with $p16^+$ oropharyngeal tumors are less likely to have a persistent viable tumor in neck lymph nodes after (chemo)radiotherapy and hypothesized that a post-treatment planned neck dissection may perhaps be avoided in $p16^+$ patients.

In conclusion, several authors indicate that the impact of HPV status must be evaluated in prospective clinical trials and included as a stratification factor to avoid potential confusion. The current AJCC-UICC staging system for oropharyngeal cancer needs to be modified in order to better reflect different prognoses for patients with HPV^+ or HPV^- tumors and those with vegetating or infiltrating tumors.

Abbreviations

AJCC-UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer; HNSCC, head and neck squamous cell carcinomas; HPV, human papillomavirus.

Competing interests

The authors declare that they have no competing interests.

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