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Human Papillomavirus: Changing Paradigms in Oropharyngeal Cancer

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Abstract The human papillomavirus (HPV) has recently been identified as an important etiologic agent in the development of squamous cell carcinoma of the oropharynx. The HPV- associated cancers appear to have a different biology than the HPV-negative cancers, and affect a population that is more likely to be young, male, Caucasian, and nonsmoking. More importantly, however, is the recognition that patients with an HPV-associated oropharyngeal cancer have a distinctly better survival after treatment than those patients with HPV-negative tumors, although their prognosis is significantly worse if there is a history of tobacco abuse. HPV-associated oropharynx cancer should be recognized as a new biologic entity and studied separately from HPV-negative cancers in future clinical trials. The potential for disease prevention with the use of the current HPV vaccines is discussed.

Keywords Human papillomavirus · Oropharynx cancer · Head and neck cancer

Introduction

It is well recognized that squamous cell carcinomas arising in the oral cavity, oropharynx, larynx, and hypopharynx result from tobacco and alcohol abuse. Other genetic, dietary, and environmental risk factors have been identified, but these are of considerably less importance [1, 2]. Recently, the human papillomavirus (HPV) has also been identified as a major etiologic agent in the development of squamous cell carcinoma of the oropharynx, including tonsil and base of tongue. These HPV-associated cancers appear to be increasing in frequency, and are affecting a different patient demographic; a younger, nonsmoking, predominately male population. Furthermore, these malignancies have a different natural history and pathogenesis and, most importantly, a better prognosis than the more common HPV-negative head and neck cancers. Identification of this subset of patients with HPV-associated oropharyngeal cancer will require a redefinition of our traditional clinical paradigms for diagnosis, treatment, and prevention of this malignancy [3••].

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HPV-Associated Oropharyngeal Cancer: Is This a Different Disease?

Epidemiology

Recent evidence suggests that the incidence of oral cavity cancer is decreasing in the United States, in sharp contrast to the increasing incidence of oropharynx cancer, most notably among younger patients [4]. The decline in oral cavity cancer has been attributed to a reduction in tobacco abuse, whereas the increasing incidence of oropharynx cancer appears to reflect a rise in HPV-related malignancy. Similar observations have been made in Europe [5]. The incidence of HPV-associated oropharyngeal cancer also varies considerably [6]. Although the worldwide estimate is 12% [7], recent data from the United States suggests that more than 60% of patients with oropharyngeal cancer may have an HPV-associated tumor [8••], an observation also reported from Sweden [9].

The human papillomavirus has also been associated with a number of other human cancers, most notably cervical

cancer in women, but also cancer of the anus, penis, and vulva [7]. The vast majority of these HPV-associated malignancies can be attributed to HPV-16, and to a lesser extent HPV-18, although a number of other less frequent HPV types have been implicated [2, 6].

As for cervical cancer, oropharyngeal HPV-associated malignancy appears to be a sexually transmitted disease [10]. Although the natural history of oral HPV infection is not well defined, it appears to be strongly associated with oropharyngeal cancer, and with a number of high-risk sexual behaviors, including a high lifetime number of vaginal sex partners, a high lifetime number of oral sex partners, and a younger age at first sexual intercourse [11••]. The recent increased incidence of this disease may then reflect societal changes in sexual behavior that have occurred over time.

Biology

HPV-associated oropharyngeal cancers appear to have a very distinct biology from the smoking and alcohol-associated HPV-negative malignancies (Table 1) [3]. In the typical squamous cell carcinoma not induced by HPV, p53 mutations are frequently found and the epidermal growth factor receptor (EGFr) is often overexpressed [12, 13]. In contrast, the HPV-related malignancies appear to result from the presence of two viral oncoproteins, E6 and E7, which inactivate the p53 and retinoblastoma (Rb) tumor suppressors. Instead of finding a mutated p53, the p53 is wild type, but inactivated in the HPV-associated malignancies. Similarly, Rb is inactivated by E7, resulting in an upregulation of p16 expression, a finding not common in the HPV-negative tumors [14]. EGFr expression has generally been reported to be low in the HPV-positive cancers [15-17], although data to the contrary also exists [18].

Pathologically, the HPV-positive tumors are often characterized as "poorly differentiated" or "basaloid." The term *basaloid* here is confusing, as it does not appear to have the same implications as a true basaloid squamous cell carcinoma, an aggressive high-grade subtype of the disease [19]. Similarly, the "poorly differentiated" nature of the malignancy reflects the fact that these are usually non-keratinizing squamous cell carcinomas, but does not carry the same implications as for other poorly differentiated head and neck squamous cell cancers. In situ hybridization appears to be the preferred method to identify HPV DNA integration into the host genome [3]. This is currently a tool available to only a limited number of institutions. P16 immunohistochemistry, however, is a readily available test, and is strongly correlated with the presence of integrated HPV DNA [20, 21].

Table 1 Molecular characteristics of HPV-positive and -negative oropharynx cancers

	HPV positive	HPV negative
p53	Wild type	Mutant
Rb	Decreased	Increased
p16	Increased	Decreased

HPV human papillomavirus

Patient Demographics

Although HPV positivity has been described in squamous cell cancers originating in oral cavity, larynx, and other head and neck subsites, more recent studies suggest that its detection is almost entirely confined to those tumors originating in tonsil and base of tongue. Patients with HPV-associated cancers tend to be younger, more frequently male and Caucasian, and have a better overall performance status. They are less frequently smokers and their tumors tend to be associated with less initial local extent (T) and greater regional disease (N) at presentation [8••, 13]. It is very common to find a large necrotic and or cystic nodal mass in the presence of a very small and often occult tonsil or base of tongue primary.

Response to Treatment

Multiple retrospective case series have suggested an improved overall prognosis in patients with HPV-associated head and neck cancer [3••, 14, 17, 22]. This improvement has been observed irrespective of the kind of treatment chosen. A recent meta-analysis of these series has been reported and has suggested that patients with HPV-positive oropharyngeal cancer have a 28% reduced risk of death and a 49% reduced risk of treatment-failure compared with patients with HPV-negative oropharyngeal tumors [23•].

Thus far, there have been three published analyses from prospective clinical trials that have evaluated the impact of HPV status on outcome. The Eastern Cooperative Oncology Group reported a series of patients treated with induction chemotherapy followed by concurrent chemoradiotherapy for both oropharynx and larynx cancer [8••]. Among the oropharynx cancer patients, 63% proved to be HPV positive and HPV positivity was not identified in any of the larynx patients. HPV-positive patients had a younger median age, were more frequently male and Caucasian, were less commonly smokers, and had a statistically better performance status than the HPV-negative patients. The response to induction chemotherapy proved statistically better in those patients with HPV-positive tumors, as was the overall survival, with a projected 2-year overall survival

of 95% compared with 62% in the HPV-negative patients (P=0.005). Similar findings were reported from a University of Michigan study assessing induction chemotherapy followed by chemoradiotherapy in responders [24•], and in an analysis of the control population from the Danish Head and Neck Cancer Group (DAHANCA) 5 trial who were treated with conventionally fractionated radiation therapy alone [25]. None of these trials, however, were of sufficient size to determine whether the improved survival in the HPV-positive patients was independent of the other important favorable prognostic features associated with HPV positivity, including age, performance status, and smoking status.

Gillison et al. [26] have conducted an analysis of the effect of tumor HPV status on survival outcomes in RTOG 0129, a study comparing concurrent cisplatin and radiation therapy using either conventional fractionation or an accelerated fractionation treatment schedule. These results were reported at the 2009 Annual Meeting of the American Society of Clinical Oncology [26]. Among the oropharynx cancer patients, 64% were found to have HPV-positive tumors. It is also of note that 96% of the HPV-positive tumors were also p16 positive on immunohistochemistry.

Similar to the Eastern Cooperative Oncology Group trial, patients with HPV-positive tumors were younger, more frequently Caucasian, and had a better performance status. HPV-positive tumors were associated with a lower T and significantly less smoking. Again, the overall survival was dramatically better in the HPV-positive patients. When a multivariable analysis was conducted, the prognostic importance of HPV status was independent of all other important prognosticators including race, T, N, age, and smoking.

Of significant interest in this study was the apparent interaction between smoking and HPV status (Table 2). The 2-year projected overall survival for those patients who were HPV-positive nonsmokers was 95%, compared with a 63% 2-year overall survival projection for the HPV-negative smokers. HPV-positive smokers and HPV-negative nonsmokers had a similar 2-year survival projection between 71% and 80%. If survival was analyzed by p16 positivity rather than HPV positivity, the predictive value of p16 positivity was equal if not better. It should also be noted that the likelihood of a second primary malignancy was statistically less in HPV-positive patients, a likely reflection of the increased incidence of nonsmokers in this population.

Therefore, what emerges is the recognition of several distinct subpopulations of patients with oropharynx cancer, who have unique prognoses after treatment. Those nonsmoking patients with HPV-positive tumors do remarkably well, with a 2-year expected survival in excess in 90%. Those smoking patients with HPV-negative tumors have a distinctly inferior 2-year survival of about 60%. Intermediate between these two groups are the nonsmoking patients with HPV-negative tumors, and the smokers with HPV-positive malignancies. Similar findings have been reported from the Netherlands in a study by Hafkamp et al. [27].

Implications for Clinical Trials

Interpretation of Historical Data

With the recognition of the increasing frequency of HPV-associated oropharyngeal cancer with a significantly better prognosis, one must consider the possibility that some of the recent progress made in the treatment of this disease may only reflect its changing natural history. Although it is tempting to attribute recent improvements in overall survival to the addition of chemotherapy, in increasingly aggressive schedules and combinations, this may not reflect the entire story. Clearly any comparison of the results from current clinical trials to historical experience is likely invalid. Given our changing expectations in this disease, concurrent control populations must be incorporated into the design of future clinical trials.

Future Clinical Trials

Although current concomitant chemoradiotherapeutic approaches in squamous cell head and neck cancer have produced significant improvements in overall survival compared with radiation therapy alone [28], this improvement comes at the cost of an associated increase in both acute and long-term toxicity [29]. Clearly, when the treatment goal is cure, both physicians and patients are more accepting of any increase in toxicity resulting from that treatment [30]. However, when the overall projected survival exceeds 90%, as in the HPV-positive nonsmoking oropharynx cancer patients, it becomes a legitimate question as to whether the toxicity is justifiable, and whether the treatment might be excessive.

The suggestion has therefore been made that this difference in prognosis between HPV-positive and HPV-negative oropharynx cancer patients must require, at the minimum, a stratification of future clinical trials for this prognostic feature. Given the dramatic differences in prognoses, however, perhaps it is more appropriate to identify different treatment goals for these populations (Table 2) [3••].

For those nonsmoking patients with HPV-positive disease and an excellent prognosis regardless of treatment used, it seems reasonable to consider the possibility of treatment "de-intensification." The hope would be that less

Table 2 HPV-based treatment goals in oropharynx cancer

Patient type	2-year overall survival [26]	Treatment goal
HPV-positive nonsmoker	95%	Reduce late effects
HPV negative or smoker	71%–80%	Improve survival
HPV negative and smoker	63%	Improve survival

HPV human papillomavirus

intensive treatment will produce less acute and late toxicity, an improved functional outcome, and a better quality of life, without any compromise in clinical efficacy. Those patients with a history of smoking and/or HPV-negative disease, however, continue to require more innovative and/or more aggressive therapies with the hope of improving their ultimate outcome. Given the strong association of tobacco abuse with squamous cell cancer arising in other head and neck sites, including oral cavity, larynx, and hypopharynx, it may be reasonable to include patients with primary tumors of these subsites together with the poorer prognosis HPV-negative oropharynx cancer patients.

There are immediate and practical concerns that result from subdividing the head and neck cancer population. This is not a common disease and only limited numbers of these patients are available for clinical trial. Increasingly, we recognize the importance of subsite-specific clinical studies, and further subdivision based on HPV status only restricts the number of questions that can be asked and the power of any conclusions that can be drawn from these studies. It is also increasingly important that we become more sophisticated in our end point evaluation. Although survival remains the gold standard end point, which must not be compromised by any treatment de-intensification, a careful assessment of early and late toxicity, functional outcomes, and patient-reported quality of life will require robust instruments capable of identifying meaningful clinical differences.

It must also be pointed out that although these HPV-based prognostic differences are dramatic, data do not yet exist that allow us to modify treatment standards of care. The hypotheses suggested by these data are compelling and certainly justify the kinds of experimental approaches discussed. However, retrospective or unplanned subset analyses do not equate with evidence-based medicine. Carefully designed prospective clinical trials are in development and will need to be completed before treatment recommendations can be made.

Implications for Prevention

There are currently two prophylactic HPV vaccines that are commercially available and have been demonstrated to decrease the incidence of precancerous lesions of the uterine cervix [31••, 32••]. The quadrivalent preparation currently available in the United States was initially approved for young women between 9 and 26 years of age for the prevention of cervical cancer, genital warts, cervical adenocarcinoma insitu, and cervical, vulvar, and vaginal intraepithelial neoplasia.

Because both commercially available vaccines protect against HPV-16, the most common HPV type implicated in oropharynx cancer, it would seem likely that these vaccines might also protect against HPV-positive oropharynx cancer [33]. Given the relatively infrequent incidence of this malignancy, however, it seems unlikely that a clinical trial can be conducted to demonstrate efficacy for this indication. Nonetheless, a compelling case can be made for universal HPV vaccination of all young men and women in the United States [34].

Conclusions

It is well established that the human papillomavirus is an important etiologic agent for squamous cell cancers of the base of tongue and tonsil. HPV-associated oropharynx cancer is a disease that is different from those oropharynx cancers and other head and neck cancers caused by tobacco and alcohol exposure. It has a distinct biology, natural history, epidemiology, and prognosis, and merits a separate approach to treatment. Future clinical trials are being developed based on HPV status. For those patients with the best prognosis, it is hoped that some treatment de-intensification will result in a reduction in the late complications of current multimodality treatments schedules with no loss of efficacy. For those patients with HPV-negative disease and those patients with a history of tobacco abuse continued efforts at improving survival are indicated.

It is important to recognize that this is the first time that a molecular marker will be incorporated into decision analysis for the management of squamous cell head and neck cancer. Further efforts must continue to better identify both clinical and molecular features predictive of treatment success. Standardization and dissemination of laboratory methodology for HPV and other molecular testing is important, as is further study of the epidemiology of oral HPV infection, and definition of strategies for screening and prevention.

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