New Chapter in Our Understanding of Human Papillomavirus-Related Head and Neck Cancer

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Our knowledge about the relationship between human papillomavirus (HPV) and squamous cell upper aerodigestive track cancers has advanced considerably over the last decade.1,2 We now know the oropharynx is the head and neck subsite particularly vulnerable to the development of tumors attributed to prior HPV infection.2,3 HPV 16 is the most common viral subtype,4,5 with implications regarding potential preventive measures.6 The incidence of HPV-related head and neck cancer is increasing,7,8 and the epidemiology of the disease and its risk factors are better understood.5,5,9 Patients with HPV-positive versus -negative disease differ. The former are younger and more likely to be white, a nonsmoker, have disease that is more responsive to therapy and overall have a better prognosis.2,10,11 Other factors such as prior tobacco use can still adversely affect the anticipated survival outcomes of patients with HPV-related head and neck cancer.11

Patients at the initial presentation of their locoregional disease have been the focus of the work to date that has generated these and other insights. The role of HPV tumor status in the recurrent or metastatic setting, however, has received far less attention. In this regard, the article by Fakhry et al12 that accompanies this editorial represents an important contribution to a new chapter in our understanding of HPV-related head and neck tumors. Specifically, how the HPV status of a recurrent or metastatic oropharynx cancer affects anticipated prognosis, and the related implications for disease management and the evaluation of new therapies.

In their article, Fakhry et al12 present a comprehensive retrospective analysis of 181 patients who were enrolled on either Radiation Therapy Oncology Group (RTOG) 0129 or 0522 for their primary chemoradiotherapy treatment, subsequently experienced progressive disease, and in whom immunohistochemical p16 data were available as a surrogate marker for HPV status.13 With a median follow-up of 4 years after progression, time to progression (8.2 v 7.3 months, P = .67, for p16-positive v –negative tumors) and patterns of disease progression did not differ significantly based on p16 status. The central finding was a dramatic difference in median overall survival after disease progression: 2.6 years for p16-positive cases versus 0.8 years for p16-negative cases (P < .001). This impact of tumor p16 status on overall survival after progression remained robust after multivariable analysis to address potential prognostic confounders and accounted for a 52% reduction in risk of death. Of note, the application of salvage surgery was associated with a reduction in mortality of similar magnitude.12

The observed difference in median overall survival between the p16-positive and -negative groups is not entirely unexpected. The molecular underpinnings of the inferior prognosis for p16-negative tumors in the locoregional disease setting after primary treatment13,14 would be expected to remain relevant at least in part in the recurrent/metastatic setting. In addition, a similar analysis by Canadian investigators who analyzed a cohort of patients with oropharynx cancer with distant spread of disease after radiation or chemoradiotherapy, found that patients with an HPV-related cancer had a better survival rate at 2 years than patients with HPV-unrelated disease (11% v 4%, P = .02).15 Based on their data, Fakhry et al12 understandably conclude that tumor HPV status should be a stratification factor in clinical trials studying patients with recurrent or metastatic oropharynx cancers.11

It has become commonplace for a number of cancers to design trials specifically for patients with tumors harboring predefined molecular characteristics. Stratification by p16 or HPV status is already occurring and expected in trials evaluating therapies for patients with previously untreated locally or regionally advanced head and neck cancers. Indeed, studies in this untreated population for which entry is limited to patients with HPV-related oropharynx cancer are in progress, evaluating, as examples, different chemoradiotherapy programs (RTOG 1016), different radiation doses after induction chemotherapy (Eastern Cooperative Oncology Group [ECOG] 1308) and primary management with transoral robotic surgery (ECOG 3311). Considering tumor HPV status and avoiding prognostic imbalance in treatment groups so as to avoid potentially misleading comparisons would seem particularly prudent when planning studies in the recurrent and metastatic setting, given that very modest improvements in survival, even in the 1- to 2-month range, have provided the basis for the approval and licensing of often expensive drugs for the treatment of advanced, refractory cancer.16

It should be emphasized, however, that the anticipated survival differences by tumor p16 or HPV status will depend on what starting point for the survival analysis is chosen. The estimated difference in typical clinical trials evaluating drug therapies for patients with recurrent or metastatic head and neck cancer may be far less than the 1.8 year difference in medians reported by Fakhry et al,12 since attempts at salvage with surgery or radiation would have likely already occurred pre-enrollment. Thus patients with a better prognosis rendered disease free by these interventions are eliminated from the denominator. Available data from the EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer)17 and SPECTRUM (Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer)18 randomized trials in patients with recurrent or metastatic disease provide insights in
this regard. Both studies evaluated a platinum doublet plus or minus an epidermal growth factor receptor antibody—cetuximab or panitumumab, respectively—and both investigated the impact of tumor p16 status on outcome. Tissue was available for testing on the majority of patients in each trial (94% and 67%, respectively). The minority of those patients with evaluable specimens had p16-positive tumors (10% and 22%, respectively). In both studies, the apparent impact of p16 status on survival was far less than the 1.8 years described in the current report. For example, in the EXTREME trial, the greatest impact of p16 status on overall survival among p16-evaluable patients was 2.9 months in the experimental arm (12.6 vs 9.7 months, p16 positive vs negative). In the SPECTRUM trial, the greatest impact of p16 status on overall survival among p16-evaluable patients was 4 months in the control arm (12.6 vs 8.6 months, p16 positive vs negative). These comparisons are limited by the small sample sizes in the p16-positive groups, the inclusion of nonoropharynx primary sites, and their derivation from subset analyses, but are nonetheless instructive. Additional clinical data sets should be forthcoming that will allow for further refinement of the impact of p16 status on overall survival in patients with recurrent or metastatic oropharynx cancer.

Studies that formally integrate tumor HPV status into their design could exploit the distinct molecular pathologies and natural histories of these two oropharynx subtypes. For example, there is preliminary clinical data that targeting PIK3CA mutated cancers has significant activity in recurrent/metastatic head and neck cancer. Although the overall burden of genetic alterations is lower in HPV-positive compared with HPV-negative head and neck cancers, targeting PIK3CA mutations appears to be higher in the former. Activating PIK3CA mutations have been described in 28% to 33% of HPV-positive oropharynx cancers, whereas the incidence of PIK3CA mutations in HPV-negative cases appears to be ≤ 10%. Because of the relative lack of genetic complexity of HPV-related oropharynx cancers, targeting of PIK3CA mutations in this disease subtype may be a more fruitful strategy than in other solid tumor types in which PIK3CA mutations commonly occur in a more complicated genetic background. Indeed, in some HPV-positive head and neck cancers, PIK3CA may be the only activating oncogenic lesion. The described genetic profiling has focused on primary tumors. Such data derived from recurrent or metastatic disease sites for the patients described in Fakhry et al’s article would be of great added interest and an important supplemental correlate to the information already provided.

Similarly, drug development efforts against the HPV E6 and E7 oncoproteins would seem indicated. In preclinical models, inhibition of E6 and E7 induces apoptosis in HPV-positive squamous cell cancer cell lines. In addition to the canonical effects of E6 on p53, other functions of E6 may be targeted in the context of HPV-specific recurrent disease studies. For example, the E6 oncoprotein activates cap-dependent translation, and this may also be associated with the oncogenic potential of the virus. Novel strategies to inhibit aberrant cap-dependent protein translation may be well suited for clinical development in HPV-related cancers. Because of shared underlying HPV biology, there is an opportunity for collaborative development of research strategies among investigators across the spectrum of HPV-related malignancy (eg, anogenital cancers).

For HPV-negative tumors, the need for innovative clinical studies is underscored by the more disappointing survival times described in this report. Refinement of epidermal growth factor receptor-targeting strategies may yield therapeutic advantage. In a phase II study, a 26% (6 of 23) major response rate for cetuximab monotherapy was observed among patients with recurrent or metastatic oral cavity or larynx cancer, typically HPV-negative sites, while no patients with oropharynx cancer responded. Subgroup analysis of the SPECTRUM study similarly suggested that the clinical benefit of adding panitumumab to conventional chemotherapy may be associated with p16-negative status. While the EXTREME study noted improvement in survival with the addition of cetuximab in both p16/HPV-related and -unrelated subsets, the improvement in the HPV-unrelated group was more convincingly demonstrated given the far larger sample size. For example, among 266 patients who were p16-negative/HPV-negative in the study, the incorporation of cetuximab improved median survival from 9.6 months to 6.7 months (P = .025). It deserves emphasis that such subset analyses should be interpreted cautiously, and are hypothesis generating only.

Selected prior retrospective reports have suggested that HPV-associated head and neck cancers might differ from HPV-negative cases with regards time-to-progression and patterns of failure. One large Canadian series reported that among 141 patients with oropharynx cancer who had relapsed, patients with HPV-related disease were more likely to develop distant metastases (67% vs 42% in HPV-negative cases) but less likely to have local failure (35% vs 53%) as a site of relapse after a median follow-up of 3.9 years. The current article overall does not corroborate these impressions. The patterns of disease progression and the distribution of distant metastatic sites appeared similar among patients with p16-positive and p16-negative tumors. Prospectively collected clinical data sets from groups like the RTOG that have standardized protocol follow-up and undergo auditing are a high quality source of information to address such questions. Two caveats are worth noting. Huang et al have reported that patients with HPV-positive disease have a higher likelihood of distant metastases involving multiple organs (46% vs 0%, P = .005), a claim not clearly addressed by the data presented by Fakhry et al. Also, others have reported later relapses in the HPV-positive group, and with a median follow-up in the current series of 4 years, some relapses may still yet be identified on further surveillance of the study cohort.

The current article has certain limitations. The data were obtained from two RTOG studies that were designed to address questions regarding locoregional treatment. Progressive disease was documented in 309 of 1,058 eligible patients with oropharynx cancer in these studies, but tissue was available for p16 analysis in only 181. Although the reported clinical characteristics of patients with and without known p16 status were similar, the exclusion of 41% (128 of 309) of patients warrants cautious consideration. Also, subsequent clinical management after disease progression could influence survival outcomes. No substantial data is presented regarding systemic therapy or reirradiation treatments for recurrent or metastatic disease.

Surgical salvage was an intervention that was studied, and was performed in 49 of 181 study subjects, most commonly for local or regional disease. This intervention was associated with improved overall survival on multivariable analysis (hazard ratio = 0.44; P < .001). Fakhry et al note that this is the first prospective trial to demonstrate that application of salvage surgery is independent predictor of overall survival for patients with oropharynx cancer. This impact of salvage surgery is not surprising, as the ability of surgery to salvage local or regional failure of head and neck cancer has been
widely appreciated for some time. Indeed, prospective larynx preservation studies have demonstrated the important role of salvage surgery in patients with advanced larynx or hypopharynx cancer in maintaining survival rates comparable with primary surgical management, and one would anticipate that similar salvage surgical management principles would apply to oropharynx cancers as well. The reported characteristics of patients who underwent surgical salvage did not appear to differ significantly from those of patients who did not except for a 2.6 year difference in mean age ($P = .05$). It is worth noting that one cannot fully exclude that there may have been unmeasured factors that influenced the decision to operate that might be related to prognosis. For example, more explicit information on medical comorbidity or residual toxicity from prior therapy was not provided. Nonetheless, the potential impact of salvage surgery deserves attention in the planning of trials for patients with recurrent or metastatic oropharynx cancer, and in the interpretation of trial results.

The National Comprehensive Cancer Network head and neck cancer practice guidelines represent one authoritative source of recommendations regarding surveillance strategies after completion of definitive locoregional therapy for oropharynx cancers. These guidelines currently do not customize follow-up based on tumor HPV status, and the data presented by Fakhry et al do not provide a clear basis to change these current recommendations. Although the likelihood of recurrence is greater for p16-negative patients, the time to recurrence, that most progression occurs within 3 years, and the patterns of failure were reported as similar for both p16-positive and p16-negative patients. History and careful examination of the head and neck examination are the cornerstones of such follow-up. There is insufficient data on the efficacy of salvage surgery for distant metastases at present to support more aggressive imaging in asymptomatic patients to identify distant disease spread. Some pilot data point toward there being a greater role for metastatectomy or other local ablative measures among patients with distant relapse of HPV-related disease, a subject that deserves further study. Of note, there are available data suggesting a role for customization of survivorship care based on HPV status of the tumor. For example, patients with p16/HPV-related disease on average will likely have a lower rate of second primary cancers and fewer comorbidities related tobacco or alcohol use. However, given their younger age, better prognosis, and longer survival times, they will need particular attention to potential late treatment morbidities including appropriate prevention and rehabilitation strategies. Available data also indicate that there are special emotional issues that need to be addressed in this population as well.

Although not a point of emphasis in the Fakhry et al article, data are presented noting that the odds of disease progression occurring in patients even with low-risk oropharynx cancer (HPV positive and ≤ 10 pack-years or HPV positive, > 10 pack-years, and NO-N2a) treated initially with chemoradiotherapy was still 18.6%. There is frequent discussion now regarding the potential role of treatment de-escalation to decrease toxicity in patients with HPV-related disease. These data highlight that de-escalation strategies need to be carefully designed to insure no compromise in disease control and at the present time should only be done in the context of a clinical trial.

In summary, the article by Fakhry et al provides many useful insights regarding the impact of tumor p16 status on outcomes for patients with recurrent or metastatic oropharynx cancers, with implications for trial design, drug development, patient management and counseling, and post-treatment follow-up. The investigators should be congratulated on the multidisciplinary cooperation and thoughtful planning to design the original trials in such a way to yield a rich data source that provides the basis for the findings they report. While the prognosis for patients with recurrent or metastatic cancer HPV-related oropharynx cancer is superior to that for patients with HPV-unrelated disease, it deserves emphasis that the prognosis remains quite worrisome in both groups. Of 105 patients with p16-positive tumors in the Fakhry et al study, 61 (58.1%) have died; of 76 patients with p16-negative tumors, 62 (81.6%) have died. Clearly innovative therapeutic ideas are needed to improve on these results. Better understanding the impact of markers like p16/HPV both in terms of clinical trial design and in patient management is a critical part of the strategy to achieve further progress.

**REFERENCES**


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