Competing Causes of Death and Medical Comorbidities Among Patients With Human Papillomavirus–Positive vs Human Papillomavirus–Negative Oropharyngeal Carcinoma and Impact on Adherence to Radiotherapy

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**IMPORTANCE** Survival of patients with head and neck cancer can be affected by competing causes of mortality, as well as comorbidities that result in radiation treatment interruptions.

**OBJECTIVE** To discern how differences in preexisting medical and psychosocial comorbidities potentially influence adherence to radiation therapy according to human papillomavirus (HPV) status.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective analysis at a comprehensive cancer center of 162 consecutive patients with locally advanced squamous cell carcinoma of the oropharynx treated with primary chemoradiation (n = 95) or primary surgery followed by adjuvant radiation (n = 67). Immunostaining for p16 was used to determine HPV status.

**MAIN OUTCOMES AND MEASURES** Difference in alcohol, tobacco, and marijuana use was compared between patients with HPV-positive and HPV-negative tumors, as well as the prevalence of the following comorbidities: diabetes mellitus, chronic obstructive pulmonary disease (COPD), anxiety disorder, and major depression. The number of total missed treatment days was analyzed as both a continuous and categorical variable.

**RESULTS** Rates of self-reported heavy alcohol use (47% vs 16%; \( P = .02 \)) and any marijuana use (47% vs 23%; \( P = .003 \)) were significantly higher among HPV-negative patients. Fifty-four percent of HPV-positive patients self-identified as never smokers, compared with only 12% of HPV-negative patients (\( P < .001 \)). HPV-negative patients had more missed treatment days (mean, 2.8 vs 1.7 days; \( P = .02 \)), as well as an increased rate of at least 5 missed days (24% vs 10%; \( P = .04 \)), and higher prevalences of COPD (12% vs 7%; \( P = .37 \)) and anxiety disorder (12% vs 6%; \( P = .35 \)).

**CONCLUSIONS AND RELEVANCE** Pronounced differences exist in lifestyle habits between patients with HPV-negative and HPV-positive oropharyngeal cancer at diagnosis. These differences, as well as those of medical and psychosocial burden, may contribute to observed discrepancies in treatment adherence and need to be considered in outcomes reporting and clinical trial design.
Patients with human papillomavirus (HPV)-positive oropharyngeal cancer tend to be younger and more commonly never-smokers than their counterparts with HPV-negative cancer. Separate mechanisms of carcinogenesis and distinct molecular characteristics have been proposed for each cohort, and improved clinical outcomes have been demonstrated in patients with HPV-positive compared with HPV-negative tumors. Given these differences, some investigators have advocated for classification of the two as distinctly different tumors. Although the standard treatment for HPV-positive and HPV-negative oropharyngeal cancer continues to be similar, prospective trials are under way to determine whether therapy can be stratified solely on the basis of HPV status.

However, it is increasingly recognized that comorbidity burden among patients with head and neck cancer is strongly correlated with prognosis, with mortality from nonmalignant causes in patients with head and neck cancers ranging from 15% to 35% at 5 years. Medical and psychosocial comorbidities not only serve as competing risk factors for death but also have the potential to affect adherence to radiation therapy, which may confound findings from trials investigating varying treatments. The purpose of this study was thus to analyze medical and psychosocial comorbidities among patients with HPV-positive and HPV-negative oropharyngeal cancer and to evaluate their potential influence on treatment adherence.

Results

Of the 162 patients evaluated, 111 were HPV-positive (69%) and 51 were HPV-negative (31%). The median age of the HPV-negative patients was significantly greater than that of the HPV-positive patients (58.7 vs 56.1 years; $P = .04$), and categorically, the HPV-positive cohort contained more patients younger than 50 years (8% vs 22%; $P = .04$). Significantly more HPV-positive patients than HPV-negative patients received a diagnosis of T1 disease (14% vs 36%; $P < .001$), and fewer had T4 disease (15% vs 22%; $P = .003$) and T4 disease (19% vs 41%; $P = .003$) (Table 1).

The prevalence of COPD at cancer diagnosis was greater among HPV-negative vs HPV-positive patients, although this was not statistically significant on univariate analysis (12% vs 7%, respectively; $P = .37$), with smoking status being identified as a significant confounder on multivariate analysis ($P = .04$). No significant difference between HPV-negative and HPV-positive patients was identified in the rate of diabetes mellitus (10% vs 9%; $P > .99$), major depression (10% vs 9%; $P > .99$), or anxiety disorder (12% vs 6%; $P = .35$) on univariate analysis. Self-reported heavy alcohol use (47% vs 16%; $P = .02$) and any marijuana use (47% vs 23%; $P = .003$) were both significantly higher among HPV-negative patients. Fifty-four percent of HPV-positive patients identified themselves as “never smokers,” compared with only 12% of HPV-negative patients ($P < .001$) (Table 2). The HPV-negative patients had poorer treatment adherence, missing more treatment days on average (mean, 2.8 vs 1.7 days; $P = .02$). A significant difference was also observed in adherence between the HPV-negative and HPV-positive cohorts using a cutoff threshold of 5 or more missed days of radiotherapy (24% vs 10%, respectively; $P = .03$), which retained significance on multivariate analysis ($P = .04$) when COPD, depression, anxiety, smoking status, alcohol use, and age were controlled for (Table 3). The Figure illustrates the proportion of patients missing at least 1, 2, 3, 4, and 5 days of the prescribed course of radiation therapy for oropharyngeal cancer according to HPV status.

Two-year overall survival was improved in patients with HPV-positive tumors compared with those with HPV-negative tumors (86% vs 71%; $P = .04$). A significantly higher rate of locoregional recurrence was observed in the HPV-negative cohort (30% vs 4%; $P < .001$).
Discussion

The results of the present study provide additional evidence supporting the increasingly recognized belief that HPV-positive and HPV-negative oropharyngeal cancer represent distinct entities. We found that patients with HPV-negative tumors were generally older and were more likely to engage in smoking, heavy alcohol consumption, and marijuana use. In addition, patients with HPV-negative tumors had a higher prevalence of certain medical and psychiatric conditions such as COPD and anxiety, although the results were statistically insignificant, likely because of the relatively small sample size of this analysis. We also identified significant differences in treatment adherence according to HPV status. Notably, the mean number of missed treatment days and the likelihood of missing 5 treatment days or more were approximately 65% and 150% greater in HPV-negative patients compared with HPV-positive patients, respectively, even when other factors were controlled for.

Recent literature has established fundamental differences in treatment outcomes, epidemiology, and molecular tu-
Differences in baseline medical and psychosocial comorbidities may influence outcome as well. 14-18 Studies have suggested that HPV-positive tumors are inherently more radiosensitive than HPV-negative tumors, our findings suggest that differences in baseline medical and psychosocial comorbidities may influence outcome as well.

The rapid repopulation of tumor cells in response to the substantial depletion that occurs during fractionated radiation is the mechanism thought to be responsible for the inferior locoregional control and overall survival associated with treatment delay. 19-21 Both radiobiological and clinical data have demonstrated that total dose, dose per fraction, and time of treatment delivery are important, interdependent factors in long-term control and survival, with temporal delays of treatment delivery being increasingly predictive of poorer outcomes. 15,22-23 Studies have suggested that even a single missed treatment day is estimated to decrease locoregional control by 1.4% to 1.6% for patients with squamous cell carcinoma of the head and neck. 14,24 On the basis of these data, the threshold that we used in the present study of at least 5 missed treatment days may represent a 7% to 8% decrease in locoregional control, which we considered to be clinically significant.

It is likely that the tendency to miss treatment is related to an inability to cope with the intense, curative radiation regimens typically prescribed for head and neck cancers. Consideration of patient characteristics, age, comorbidities, habits, management of the toxic effects of treatment, and psychosocial burden, in addition to tumor stage, prognosis, and performance status, may be beneficial in individualizing treatment intensity.

Of similar importance, treatment adherence and contributing factors should be considered in the design of clinical trials and the interpretation of published data documenting differences in outcome between HPV-positive and HPV-negative cancers. Modification of clinical trial design has recently been suggested to account for competing causes of mortality. 11 Also accounting for the proportion of worsened outcomes attributable to treatment interruptions may be useful.

Our findings require verification because the primary limitation of the present study was its retrospective design. In addition, the specific reason why patients missed treatment days was not always determined with certainty. Toxic effects of radiation therapy, which can contribute to patient adherence to treatment, were not specifically evaluated. Pain levels were not routinely recorded, and the identification of psychosocial burden was limited to diagnoses identified within the medical record and generally did not include comprehensive psychiatric evaluation. Heavy, moderate, and rare alcohol use were determined by means of patient questionnaire and not objectively quantified. Other comorbidities, including coronary artery disease, non-COPD pulmonary etiologies, and so forth,
were not comprehensively assessed with the Charlson Comorbidity Index or any other quantitative measurement of comorbidity profile.

Despite the fact that increases in overall treatment time for head and neck cancers have been associated with poorer outcomes, it remains speculative whether patients with HPV-negative tumors who are at risk for nonadherence should be considered for accelerated treatment through hyperfractionated, hypofractionated, or concomitant-boost regimens in an attempt to compensate for missed fractions. Whereas these alternative strategies are not routinely performed, we advocate that decisions regarding treatment modification for nonadherence be made on a case-by-case basis considering such factors as medical and psychosocial comorbidities in conjunction with performance status and prognosis.

Conclusions

Human papillomavirus–negative oropharyngeal cancer has generally been shown to convey worse overall survival and locoregional control when compared with HPV-positive cancer. However, patients with HPV-negative oropharyngeal cancer also carry a much higher burden of competing risk factors for death, likely as a result of presenting at an older age and with more extensive histories of tobacco, alcohol, and/or marijuana use. This population is also more likely to experience delays and interruptions in prescribed radiation therapy. Treatment adherence, in addition to competing mortality risk, needs to be considered in outcome reporting and the design of clinical trials addressing these populations in the future.