UCSF

Title

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

Authors

Hess, Clayton B
Rash, Dominique L
Daly, Megan E
et al.

Peer reviewed

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

Clayton B. Hess, MD,
Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento

Dominique L. Rash, MD,
Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento

Megan E. Daly, MD,
Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento

D. Gregory Farwell, MD,
Department of Otolaryngology–Head and Neck Surgery, University of California Davis Comprehensive Cancer Center, Sacramento

John Bishop, MD,
Department of Pathology, University of California Davis Comprehensive Cancer Center, Sacramento

Andrew T. Vaughan, PhD,
Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento

Corresponding Author: Allen M. Chen, MD, Department of Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, 200 Medical Plaza B265, Los Angeles, CA 90095 (amchen@mednet.ucla.edu).

Machelle D. Wilson, PhD, and

Division of Biostatistics, Department of Public Health Sciences, University of California Davis School of Medicine, Sacramento

Allen M. Chen, MD

Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento

Abstract

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.[1–3] 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.[4–6] Given these differences, some investigators have advocated for classification of the two as distinctly different tumors.[1,7] 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.[8–10]

However, it is increasingly recognized that comorbidity burden among patients with head and neck cancer is strongly correlated with prognosis,[3] with mortality from nonmalignant causes in patients with head and neck cancers ranging from 15% to 35% at 5 years.[11–13] 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.

Methods

Institutional review board (IRB) approval was obtained from the University of California, Davis, School of Medicine prior to the review of all medical records and patient information. A waiver for consent was obtained from the IRB because of the retrospective nature of this work. The medical records of 162 consecutive patients (142 men, 20 women) with locally advanced (stage III or IV) squamous cell carcinoma of the oropharynx, with known p16 status, treated by means of primary cisplatin-based chemoradiation (n = 95) or primary surgery followed by adjuvant radiation therapy (n = 69) from 2006 to 2013 were reviewed. All patients had Karnofsky Performance Status greater than 70. Heavy, moderate, and rare alcohol use were subjectively defined and assigned by patient self-report. Concurrent cisplatin was administered either at 100 mg/m^2 every 3 weeks for 3 cycles or alternatively at 50 mg/m^2 on weeks 1, 2, 4, and 5 with radiation therapy. Overexpression of p16 (which was used as a surrogate of HPV) was defined as tumors that displayed intense diffuse cytoplasmic and nuclear staining in more than 70% of tumor cells using a monoclonal antibody against p16.

Differences in the prevalences of the following preexisting, medical comorbidities and lifestyle habits between the 2 cohorts at cancer diagnosis were compared by means of univariate analysis: diabetes mellitus, chronic obstructive pulmonary disease (COPD), anxiety disorder, and major depressive disorder, as well as alcohol, tobacco, and marijuana use. Comorbidities were established by means of retrospective review of patient intake questionnaires completed at the time of initial consultation. Multivariate analysis was subsequently performed considering significant variables as identified on univariate analysis. Missed treatment days (excluding holidays or machine breakdown) was analyzed as both a categorical (5 or more missed appointments) and continuous (total number missed) outcome variable using multivariate regression (logistic or linear) controlling for age (older or younger than 50 years), COPD, depression, anxiety, smoking history, and alcohol use. P < .05 was used for statistical significance. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute).

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 T3 (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 tumor characteristics between HPV-positive and HPV-negative oropharyngeal cancers.[1–7] Medical comorbidities can lead to competing causes of mortality,[3,11–13] and treatment interruptions have been strongly associated with worse outcomes,[14–18] but the role of each in the setting of HPV-related head and neck cancer is still uncertain. Our findings, demonstrating fairly pronounced differences in medical and psychosocial burden at diagnosis, as well as treatment adherence, between these 2 cohorts, are noteworthy for their potential to confound the previously reported improved outcomes among HPV-positive patients. To our knowledge, this is the first report correlating HPV status with discrepancies in patient adherence to daily radiation treatments. Although 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 non-adherence 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 cancers 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.

Acknowledgments

References

1. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008; 100(6):407–420. [PubMed: 18334711]

2. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. Head Neck. 2008; 30(1):75–84. [PubMed: 17694557]

3. Yung KC, Piccirillo JF. The incidence and impact of comorbidity diagnosed after the onset of head and neck cancer. Arch Otolaryngol Head Neck Surg. 2008; 134(10):1045–1049. [PubMed: 18936348]

4. O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis. Oral Oncol. 2012; 48(12):1191–1201. [PubMed: 22841677]

5. Sartor MA, Dolinoy DC, Jones TR, et al. Genome-wide methylation and expression differences in HPV(+) and HPV(−) squamous cell carcinoma cell lines are consistent with divergent mechanisms of carcinogenesis. Epigenetics. 2011; 6(6):777–787. [PubMed: 21613826]

6. Wittekindt C, Wagner S, Mayer CS, Klussmann JP. Basics of tumor development and importance of human papilloma virus (HPV) for head and neck cancer. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2012; 11:Doc09. [PubMed: 23320061]

7. Klussmann JP, Weissenborn SJ, Wieland U, et al. Human papillomavirus-positive tonsillar carcinomas: a different tumor entity? Med Microbiol Immunol. 2003; 192(3):129–132. [PubMed: 12920586]

8. Boscolo-Rizzo P, Del Mistro A, Bussu F, et al. New insights into human papillomavirus-associated head and neck squamous cell carcinoma. Acta Otorhinolaryngol Ital. 2013; 33(2):77–87. [PubMed: 23853396]

9. Psyrri A, Sasaki C, Vassilakopoulou M, Dimitriadis G, Rampias T. Future directions in research, treatment and prevention of HPV-related squamous cell carcinoma of the head and neck. Head Neck Pathol. 2012; 6(suppl 1):S121–S128. [PubMed: 22782231]

10. Brotherston DC, Poon I, Le T, et al. Patient preferences for oropharyngeal cancer treatment de-escalation. Head Neck. 2013; 35(2):151–159. [PubMed: 22431201]

11. Mell LK, Dignam JJ, Salama JK, et al. Predictors of competing mortality in advanced head and neck cancer. J Clin Oncol. 2010; 28(1):15–20. [PubMed: 19933920]

12. Rose BS, Jeong JH, Nath SK, Lu SM, Mell LK. Population-based study of competing mortality in head and neck cancer. J Clin Oncol. 2011; 29(26):3503–3509. [PubMed: 21844503]

13. Argiris A, Brockstein BE, Haraf DJ, et al. Competing causes of death and second primary tumors in patients with locoregionally advanced head and neck cancer treated with chemoradiotherapy. Clin Cancer Res. 2004; 10(6):1956–1962. [PubMed: 15041712]

14. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiat Oncol Biol Phys. 2007; 68(3):654–661. [PubMed: 17467926]

15. Fesinmeyer MD, Mehta V, Blough D, Tock L, Ramsey SD. Effect of radiotherapy interruptions on survival in Medicare enrollees with local and regional head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2010; 78(3):675–681. [PubMed: 20133084]

16. Herrmann T, Baumann M. Prolongation of latency or overall treatment time by unplanned radiation pauses: the clinical importance of compensation [in German]. Strahlenther Onkol. 2005; 181(2):65–76. [PubMed: 15702294]

17. Lindberg RD, Jones K, Garner HH, Jose B, Spanos WJ Jr, Bhatnagar D. Evaluation of unplanned interruptions in radiotherapy treatment schedules. Int J Radiat Oncol Biol Phys. 1988; 14(4):811–815. [PubMed: 3350733]

18. Wyatt RM, Beddoe AH, Dale RG. The effects of delays in radiotherapy treatment on tumour control. Phys Med Biol. 2003; 48(2):139–155. [PubMed: 12587901]

19. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001; 51(3):571–578. [PubMed: 11597795]

20. Byers RM, Clayman GL, Guillamondequi OM, Peters LJ, Goepfert H. Resection of advanced cervical metastasis prior to definitive radiotherapy for primary squamous carcinomas of the upper aerodigestive tract. Head Neck. 1992; 14(2):133–138. [PubMed: 1601650]

21. Garden AS, Weber RS, Ang KK, Morrison WH, Matre J, Peters LJ. Postoperative radiation therapy for malignant tumors of minor salivary glands: outcome and patterns of failure. Cancer. 1994; 73(10):2563–2569. [PubMed: 8174054]

22. Bourhis J, Overgaard J, Audry H, et al. MARCH Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006; 368(9538):843–854. [PubMed: 16950362]

23. Baujat B, Bourhis J, Blanchard P, et al. MARCH Collaborative Group. Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane Database Syst Rev. 2010; (12):CD002026. [PubMed: 21154350]

24. Hendry JH, Bentzen SM, Dale RG, et al. A modelled comparison of the effects of using different ways to compensate for missed treatment days in radiotherapy. Clin Oncol (R Coll Radiol). 1996; 8(5):297–307. [PubMed: 8934049]
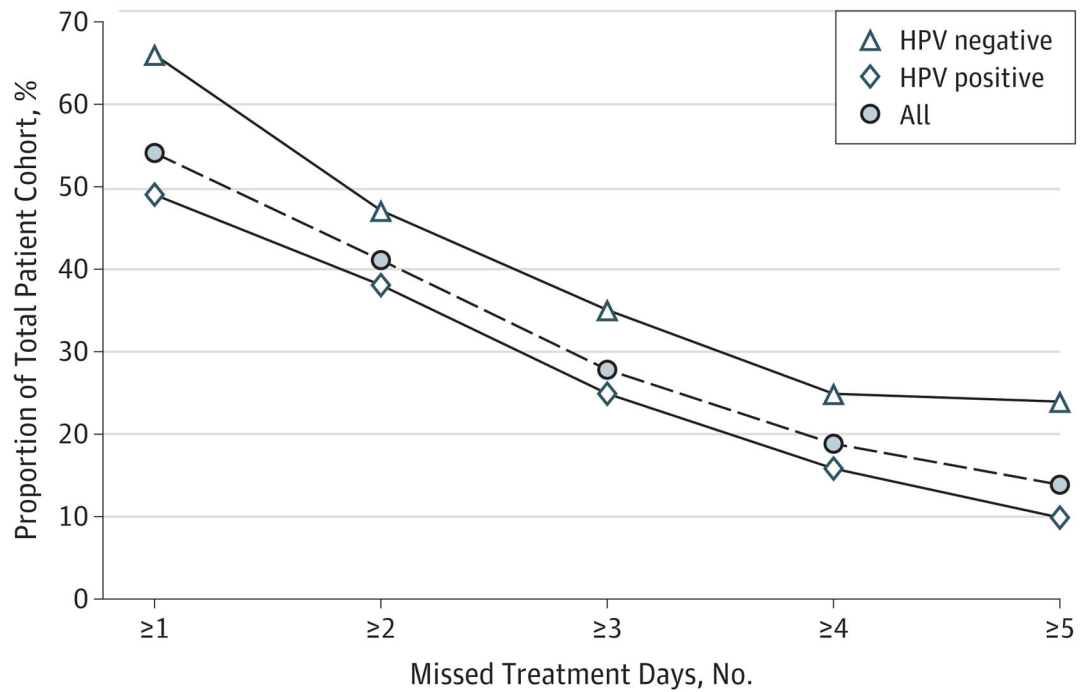
Figure.

Patients Missing Radiation Therapy Treatments for Oropharyngeal Cancer According to Human Papillomavirus (HPV) Status

Proportion of patients who missed at least 1, 2, 3, 4, and 5 days of the prescribed course of radiation therapy according to HPV status of their oropharynx cancer.

Table 1

Patient Characteristics

Characteristic	Patients		P Value[a]	Total (N = 162)
	HPV Negative (n = 51)	HPV Positive (n = 111)		
Male sex, No. (%)	45 (88)	97 (87)	>.99	142 (88)
Age, mean (range), y	58.7 (45–74)	56.1 (38–74)	.04	56.9 (38–74)
Age <50 y, No. (%)	4 (8)	24 (22)	.04	28 (17)
T stage, No. (%)			.003	
T1	7 (14)	40 (36)	<.001[b]	47 (29)
T2	12 (24)	33 (30)	.99[b]	45 (28)
T3	11 (22)	17 (15)	.003[b]	28 (17)
T4	21 (41)	21 (19)	.003[b]	42 (26)
N stage, No. (%)			.74	
N0	2 (4)	4 (4)	NP	6 (4)
N1	2 (4)	13 (12)	NP	15 (9)
N2a	4 (8)	8 (7)	NP	12 (7)
N2b	21 (41)	45 (41)	NP	66 (41)
N2c	15 (29)	28 (25)	NP	43 (27)
N3	7 (14)	13 (12)	NP	20 (12)
M stage, No. (%)				
M1	0	2 (2)	NP	2 (1)
Treatment			.86	
Definitive RT, No. (%)	29 (57)	66 (59)	NP	95 (59)
Surgery with adjuvant RT, No. (%)	22 (43)	45 (41)	NP	67 (41)
Total RT dose, mean (IQR), cGy	6648 (6600–7000)	6683 (6600–7000)	NP	6629 (6600–7000)
Concurrent chemotherapy, No. (%)	41 (80)	88 (79)	.57	129 (80)
Follow-up, mean (IQR), mo	31.2 (9.1–46.6)	36.9 (14.5–54.5)	NP	35.2 (13.2–50.2)

Abbreviations: HPV, human papillomavirus; IQR, interquartile range; NP, analysis not performed; RT, radiotherapy.

[a]Univariate analysis using Fisher exact test for categorical data and unpaired *t* test for continuous data unless otherwise indicated.

[b]Multivariate analysis (controlling for diabetes mellitus and smoking history).

Table 2

Patient Comorbidities

	Patients		
Comorbidity	HPV Negative (n = 51)	HPV Positive (n = 111)	P Value[a]
COPD, No. (%)	6 (12)	8 (7)	.37
Tobacco use, mean, pack-years	46.8	25.7	<.001
Alcohol use, No. (%)			<.001
Heavy	24 (47)	18 (16)	.02[b]
Moderate	15 (29)	34 (31)	.001[b]
Rare	6 (12)	35 (32)	.23[b]
None	6 (12)	24 (22)	<.001[b]
Marijuana use, No. (%)	24 (47)	26 (23)	.003
Diabetes mellitus, No. (%)	5 (10)	10 (9)	>.99
Major depressive disorder, No. (%)	5 (10)	10 (9)	>.99
Anxiety disorder, No. (%)	6 (12)	7 (6)	.35
Never smoker, No. (%)	6 (12)	60 (54)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; HPV, human papillomavirus.

[a] Univariate analysis using Fisher exact test for categorical data and unpaired *t* test for continuous data unless otherwise indicated.

[b] Multivariate analysis (controlling for diabetes mellitus, marijuana use, COPD, and smoking history).

Table 3

Treatment Adherence

Days Missed	Patients		P Value[a]	Total (N = 162)
	HPV Negative (n = 51)	HPV Positive (n = 111)		
No. (%)				
1	34 (66)	54 (49)	NP	88 (54)
2	24 (47)	42 (38)	NP	66 (41)
3	18 (35)	28 (25)	NP	46 (28)
4	13 (25)	18 (16)	NP	31 (19)
5	12 (24)	11 (10)	.04[b]	23 (14)
Mean	2.8	1.7	.02[c]	…

Abbreviations: COPD, chronic obstructive pulmonary disease; HPV, human papillomavirus; NP, analysis not performed.

[a] Univariate analysis using Fisher exact test for categorical data and unpaired *t* test for continuous data unless otherwise specified.

[b] Multivariate logistic regression analysis (controlling for age <50 years, COPD, depression, anxiety, smoking history, and alcohol use).

[c] Multivariate linear regression analysis (controlling for age <50 years, COPD, depression, anxiety, smoking history, and alcohol use).