Prevalence and predictive role of p16 and epidermal growth factor receptor in surgically treated oropharyngeal and oral cavity cancer

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ABSTRACT: *Background.* The purpose of this study was to describe the relationship of p16 and epidermal growth factor receptor (EGFR) expression with survival in surgically treated patients who had oropharyngeal or oral cavity squamous cell carcinoma (SCC).

Methods. Tissue from 36 patients with oropharyngeal SCC and 49 patients with oral cavity SCC treated between 1997 and 2001 was imbedded and immunostained using a tissue microarray.

Results. The p16 was positive in 57% and 13% of patients with oropharyngeal SCC and oral cavity SCC, respectively. EGFR was positive in 60% and 63% of patients with oropharyngeal SCC and oral cavity SCC, respectively. In patients with oropharyngeal SCC, p16 expression was associated with improved disease-specific survival (DSS), overall survival (OS), and time to recurrence (TTR) ($p < .01$, $< .01$, and $< .01$, respectively). EGFR expression was associated with poorer DSS, OS, and TTR ($p < .01$, $= .01$, and $< .01$, respectively). For oropharyngeal SCC, when examining both p16 and EGFR expression as combined biomarkers, high p16 expression coupled with low EGFR expression was associated with improved DSS (p p16 $= .01$; p EGFR $= .01$). Patients with oral cavity SCC showed no association between biomarker and outcome.

Conclusions. For patients with oropharyngeal SCC, high p16 and low EGFR were associated with improved outcome, suggesting a predictive role in surgically treated patients. © 2012 Wiley Periodicals, Inc. *Head Neck* **35:** 1083–1090, 2013

KEY WORDS: oropharyngeal neoplasm, oral cavity neoplasm, p16(INK4A), EGFR protein, human papillomavirus

INTRODUCTION

Optimal treatment of oropharyngeal and oral cavity squamous cell carcinoma (SCC) should be guided by both patient characteristics and tumor biology. Conventional treatment of locally advanced oropharyngeal and oral cavity SCC involves multimodality therapy, which includes a combination of surgery, radiotherapy, and cisplatin-based chemotherapy. Primarily, clinical factors guide decisions on the type of treatment prescribed to the patient. More recently, however, prognostic biological markers, in addition to clinical parameters, have improved the ability to predict outcome, particularly in patients with oropharyngeal SCC. Among them, expression of p16 and epidermal growth factor receptor (EGFR), assessed through immunohistochemistry, have been shown to help further characterize the behavior of tumors and ultimately may aid in the design of clinical trials that will select patients requiring treatment escalation or de-escalation.

P16 is an excellent surrogate marker for high-risk human papillomavirus (HPV) in patients with oropharyngeal SCC, reflecting the inactivation of the retinoblastoma tumor suppressor protein by the oncoprotein E7.[1] Many studies have demonstrated the correlation between p16 expression and improved survival, particularly in patients with oropharyngeal SCC and particularly in those treated with nonsurgical therapies.[1–3] EGFR plays an important role in the regulation of cellular proliferation and survival in epithelial tumors. Alterations in EGFR signaling pathways lead to decreased apoptosis of tumor cells, enhanced invasiveness, cell migration, angiogenesis, and metastasis.[4] Many studies have demonstrated an association between elevated expression of EGFR and poorer survival, although the majority of these studies focus on nonsurgical treatment of patients with oropharyngeal SCC.[2,3,5,6]

At the University of Michigan, standard treatment for patients with locally advanced oropharyngeal SCC includes a combination of chemotherapy and radiotherapy. A recent trial (UMCC-9921) demonstrated the

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efficacy of both p16 and EGFR in predicting survival in patients with oropharyngeal SCC treated with nonsurgical modalities.[2] Patients with increased expression of p16 had improved survival, whereas those with elevated expression of EGFR had poorer survival. Less is known about the ability of these biomarkers to predict outcome in patients with oropharyngeal SCC who are treated surgically. Furthermore, the ability of these biomarkers to predict survival in patients with oral cavity SCC has yet to be investigated. The purpose of this study was to evaluate and contrast biomarker expression in surgically treated patients with oropharyngeal and oral cavity SCC.

MATERIALS AND METHODS

Study design

This was a prospective cohort study.

Study population

Eligibility criteria for this study included patients with previously untreated oropharyngeal or oral cavity SCC who were treated with primary surgical extirpation. Patients were excluded if they presented with a synchronous primary neoplasm of the head and neck, a history of previous head and neck cancer, a history of previous surgery or radiation therapy to the upper aerodigestive tract, or distant metastatic disease. Eighty-five patients were enrolled from 1997 to 2001 and followed prospectively for outcome (disease status and survival). These 85 patients were separated into 2 cohorts: 36 patients with oropharyngeal SCC and 49 with oral cavity SCC. These cohorts were each analyzed separately. The cohort sizes were small because of the stringent inclusion criteria. The inclusion criteria of no prior treatment limited the cohort size the most. Table 1 demonstrates baseline demographics, staging, and treatment modality of the patient cohorts with oropharyngeal and oral cavity SCC. Patients continue to undergo regular follow-up and have currently been followed for 9 years. With respect to the 36 patients who made up the oropharyngeal SCC cohort, the 5-year disease-specific survival (DSS) and overall survival (OS) were 59% and 38%, respectively. At 5 years of follow-up, 42% of patients (15 of 36) were alive and free of disease, 3% (1 of 36) were alive with disease, 36% (13 of 36) were dead of disease, 6% (2 of 36) were dead of second primary neoplasm, and 14% (5 of 36) were dead of intercurrent illness.

The 5-year DSS and OS estimates for the 49 patients with oral cavity SCC were 60% and 54%, respectively. At 5 years of follow-up, 59% of patients (29 of 49) were alive and free of disease, 29% (14 of 49) were dead of disease, 2% (1 of 49) were dead of a second primary tumor, 8% (4 of 49) were dead of intercurrent illness, and 2% (1 of 49) were lost to follow-up.

Variables under study

Patients were evaluated at baseline for clinical covariates (age, sex, tobacco exposure, alcohol history, tumor site, and stage). Tobacco history and alcohol status were classified as "never,'' "past'' (quit 6 months ago), or "current.'' Staging was based on the 2002 American Joint Committee on Cancer staging system. Pretreatment biopsies of the primary tumor were used to construct a tissue microarray to evaluate the expression of biomarkers (p16 and EGFR). After surgical extirpation, pathology specimens were evaluated for perineural/perivascular invasion, histologic grade, and nodal characteristics.

TABLE 1. Patient and tumor characteristics.

	Oral cavity SCC $n = 49$	Oropharyngeal SCC $n = 36$
Age: mean (SD)	57.2 (17.0)	52.3 (11.0)
Sex		
Male	17 (35%)	5 (14%)
Female	32 (65%)	31 (86%)
Smoking history		
Never	3 (6%)	2 (6%)
Past	36 (73%)	29 (81%)
Current	6 (12%)	4 (11%)
Unknown	4 (8%)	1 (3%)
Adjuvant treatment		
None	15 (30%)	–
Radiotherapy	33 (66%)	31 (86%)
Chemoradiotherapy	2 (4%)	5 (14%)
T classification (clinical)		
T1	5 (10%)	1 (3%)
T2	15 (31%)	9 (25%)
T3	10 (20%)	12 (33%)
T4	19 (39%)	14 (39%)
N classification (pathologic)		
N0	22 (45%)	5 (14%)
N1	8 (16%)	4 (11%)
N2	19 (39%)	24 (69%)
N3	–	2 (6%)
AJCC stage		
I	4 (8%)	–
II	8 (16%)	–
III	9 (18%)	6 (17%)
IV	26 (57%)	30 (83%)
Histologic grade		
Well	9 (20%)	2 (6%)
Moderate	30 (65%)	19 (54%)
Poor	7 (15%)	14 (40%)
Perineural invasion	10 (20%)	4 (11%)
Perivascular invasion	7 (14%)	8 (22%)
Nodal ECS	12 (24%)	21 (58%)

Abbreviations: SCC, squamous cell carcinoma; AJCC, American Joint Committee on Cancer; ECS, extracapsular spread.

Immunostaining and scoring

Tumor specimens used to construct the tissue microarray were deparaffinized, rehydrated, and peroxidase-quenched (Dako Cytomation, Glostrup, Denmark). For antigen retrieval, slides were incubated with citrate buffer (p16; 30 minutes at 92°C) or with pepsin (EGFR; 10 minutes at 37°C) and were blocked with horse serum (30 minutes at 25°C). Primary antibody, p16/16P04, (LabVision, Fremont CA) and EGFR/31G7 (Zymed Laboratories, South San Francisco, CA), were added for 1 hour and were probed with avidin/biotin peroxidase (ABC Kit; Vector Laboratories, Burlingame, CA).[2]

Antibody binding was scored by a pathologist (K.G.C.) who was blinded to the clinical outcome. Based on previous experience from our institution,[2,7] p16 expression was scored based on the proportion of tumor staining

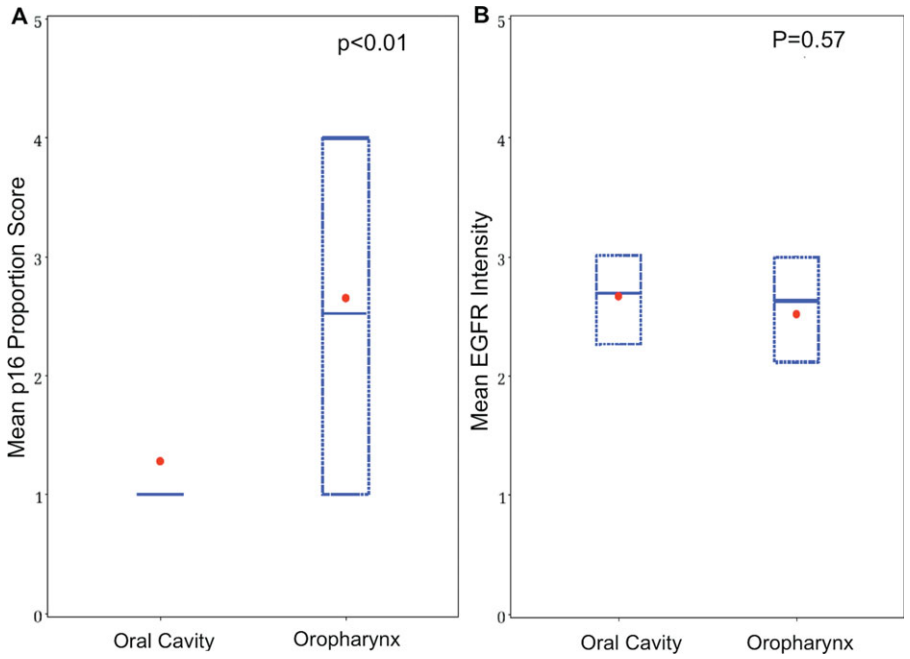

FIGURE 1. Comparison of mean score of immunostain across subsites. (A) Box plot shows a significantly lower mean score of p16 proportion in oral cavity squamous cell carcinoma (SCC) versus oropharyngeal SCC. (B) A similar mean score of epidermal growth factor receptor (EGFR) intensity is seen between oral cavity SCC and oropharyngeal SCC. Dot, mean; box, 25th to 75th percentile; horizontal bar, median. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

positive using an ordinal scale from 1 to 4: 1 was less than 5%, 2 was 5% to 20%, 3 was 21% to 50%, and 4 was 51% to 100%. Patients with a score greater than 1 were considered positive for p16. EGFR expression was scored based on the level of intensity using a scale from 1 to 4; 1 equal to no staining, 2 equal to low intensity, 3 equal to moderate, and 4 equal to high intensity. Patients with a score greater than 2 were considered positive for EGFR. Scores for 3 cores of tumor from each patient were averaged. Of the 36 patients with oropharyngeal SCC eligible for the study, 35 had sufficient specimens for immunostaining. Of the 49 patients with oral cavity SCC eligible for the study, 46 had sufficient specimens for immunostaining.

Response variables

Patients were evaluated for the following outcomes: DSS defined by the time from primary surgery to death from oral cavity SCC or oropharyngeal SCC, OS defined by the time from primary surgery to all-cause mortality, and time to recurrence (TTR) defined by the time from primary surgery to the first recurrence.

Statistical analysis

Baseline patient and tumor characteristics were tabulated. Patient-level averages for proportion of p16 expression and intensity of EGFR expression were used in the analysis. For the assessment of bivariate associations between markers and covariates, rank-based statistical methods were used. The Kaplan–Meier method and the log-rank test were used to compare the homogeneity of survival rates within and between categories of discrete variables. Only patients who had sufficient specimen for immunostaining were considered for the association between markers and survival. The Cox proportional hazards models were used to assess the markers' effects beyond the effects of the clinical covariates. Likelihood ratio statistics were used to determine statistically significant differences between the models. All statistical analyses were done with SAS version 9.0 (SAS Institute, Carey, NC). A 2-tailed p value of .05 or less was considered statistically significant.

The Institutional Review Board at the University of Michigan granted approval for this study.

RESULTS

Prevalence of p16 and epidermal growth factor receptor

The prevalence of p16 positivity in patients with oropharyngeal and oral cavity SCC were 57% (20 of 35) and 13% (6 of 46), respectively. The mean proportion of cells staining positive for p16 was higher in the oropharynx (Figure 1A; $p < .01$). Of the 20 patients who were positive for p16 in the oropharynx, 95% (19 of 20) had a p16 score of 4. In contrast, of the 6 patients who were positive for p16 in the oral cavity, only 50% (3 of 6) had a score of 4.

The prevalence of EGFR positivity in the oropharynx and oral cavity were 60% (21 of 35) and 63% (29 of 46), respectively. In addition, there was no statistically significant difference in mean intensity of EGFR staining between oropharyngeal and oral cavity tumors (Figure 1B; $p = .57$).

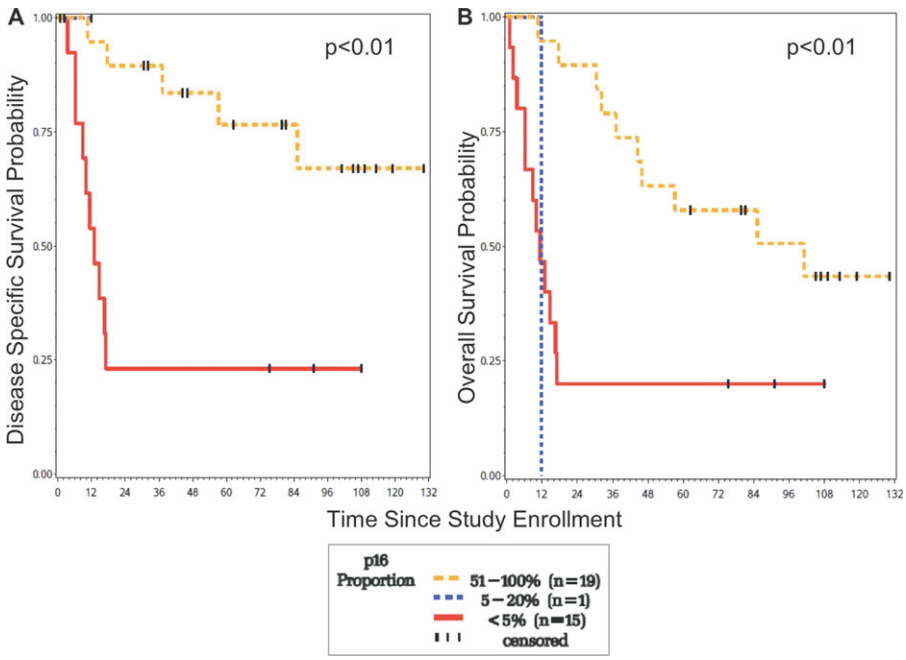

FIGURE 2. Survival of patients with oropharyngeal squamous cell carcinoma (SCC) according to p16 proportion. (A) Those with a high p16 expression have significantly improved disease-specific survival (DSS). (B) Those with a high p16 expression have improved overall survival (OS). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Biomarker and survival analysis

p16 survival analysis. For oropharyngeal SCC, patients with a higher p16 expression experienced significantly improved DSS ($p < .01$) and OS ($p < .01$) compared with those with a low p16 expression at 9 years of follow-up (Figure 2). In addition, patients with a higher p16 expression had a significantly longer TTR ($p < .01$). At 5 years, those with the highest p16 staining proportion (51% to 100%; score = 4) had a DSS of 75% versus those with a staining proportion of less than 5% (score = 1) who had a DSS of 23%. Similarly, those with the highest p16 staining proportion (51% to 100%; score = 4) had an OS of 57% versus those with a staining proportion of less than 5% (score = 1) who had an OS of 20%.

Forty-three percent of the patients (15 of 35) with oropharyngeal SCC were negative for p16 expression, and this finding was associated with a poorer DSS and OS. Of these 15 patients, 9 were dead from disease at 5 years of follow-up. The pattern of recurrence included 1 of 9 local, 1 of 9 regional, 4 of 9 distant, 2 of 9 local/regional, and 1 of 9 local/regional/distant. In summary, distant disease was seen in 5 of 9 patients with oropharyngeal SCC who were negative for p16 expression.

Of the patients with oropharyngeal SCC, 57% (20 of 35) were positive for p16 expression, and this was associated with improved survival. Of these 20 patients, 4 were dead from disease at 5 years of follow-up. Interestingly, in this group of patients who were p16-positive, all 4 died of distant disease.

In oral cavity SCC, due to the low prevalence of p16 (13%), the ability to stratify patients by this biomarker was not feasible when performing survival analysis.

Epidermal growth factor receptor survival analysis

For oropharyngeal SCC, patients with none or low EGFR expression (score = 1 or 2) experienced significantly improved DSS ($p < .01$) and OS ($p = .01$) compared with those with a moderate or high level of expression (score = 3 or 4) at 9 years of follow-up (Figure 3). In addition, patients with a lower EGFR expression had a significantly increased TTR ($p < .01$). At 5 years, those with none or low expression had a DSS of 95% versus those with a moderate or high expression, who had a DSS of 38%. Similarly, those with none or low expression had an OS of 68% versus those with a moderate or high expression, who had an OS of 25%.

Sixty percent (21 of 35) of the patients with oropharyngeal SCC were positive for EGFR expression, and this was associated with poorer DSS and OS. Of these 21 patients, 12 were dead from disease at 5 years of follow-up. Most patients died of distant disease. The pattern of recurrence was 9 of 12 distant, 2 of 12 local/regional, and 1 of 12 local recurrence.

Forty percent (14 of 35) of the patients with oropharyngeal SCC were negative for EGFR expression, and this was associated with improved DSS and OS. Of these 14 patients, only 1 died of disease at 5 years of follow-up, and this was from a regional recurrence.

Combined marker survival analysis

For oropharyngeal SCC, when examining both p16 and EGFR expression as combined markers in a multivariable model, high p16 expression coupled with low EGFR expression was associated with improved DSS (p p16 = .01; p EGFR = .01; Figure 4). At 5 years, the DSS for

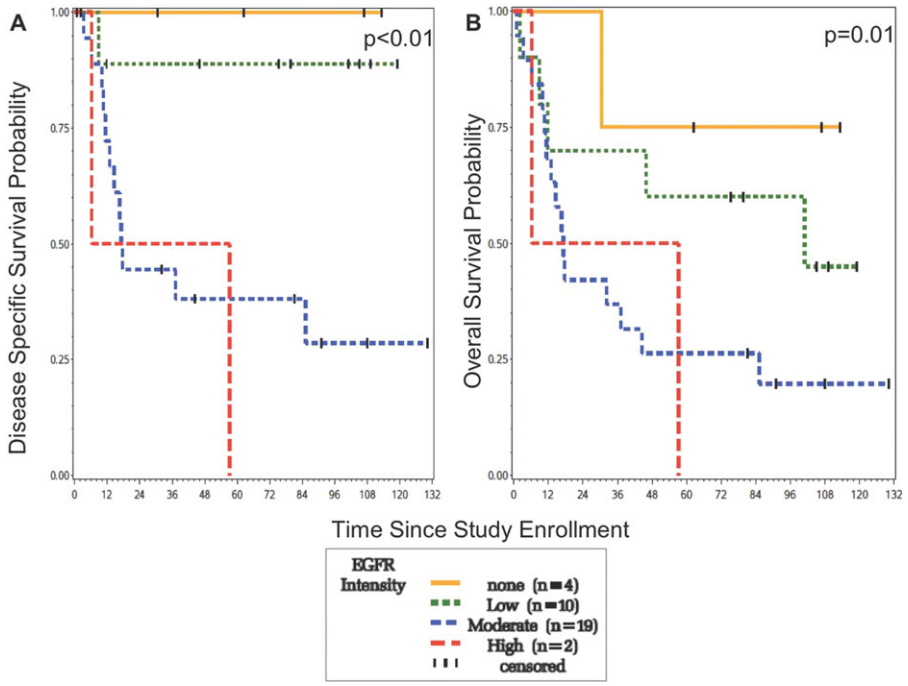

FIGURE 3. Survival of patients with oropharyngeal squamous cell carcinoma (SCC) according to epidermal growth factor receptor (EGFR) intensity. (A) Those with none or low EGFR expression have significantly improved disease-specific survival (DSS). (B) Those with none or low EGFR expression have significantly improved overall survival (OS). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the 10 patients with high p16 proportion and low EGFR intensity was 100%. In contrast, the DSS for the 12 patients with low p16 proportion and high EGFR intensity was 17%.

Clinical covariates and outcome

In patients with oropharyngeal SCC, 58% (21 of 36) had evidence of extracapsular spread in the lymph nodes and 22% (8 of 36) had evidence of perivascular invasion in the primary tumor. In univariate analysis, extracapsular spread and perivascular invasion were each associated with poorer DSS ($p = .026$ and .014, respectively). However, multivariable regression changed these findings. When a multivariable regression was performed on extracapsular spread (ECS), perivascular invasion, and EGFR, only EGFR remained a significant predictor of DSS ($p = .002$). For patients with oropharyngeal SCC, higher levels of EGFR expression were associated with a positive smoking history, either past or current ($r = 0.385$; $p = .025$; Figure 5). This finding must be tempered by the fact that of the 35 patients, the majority (29 of 35) were past smokers, whereas only 2 were never smokers and 4 were current smokers. In patients with oral cavity SCC, there was a similar lack of never smokers (3 of 45). Most patients had a smoking history (36 of 45) but were not current smokers (6 of 45).

For patients with oral cavity SCC, several clinical covariates were found to be associated with survival. On bivariate analysis, the presence of perineural invasion in the primary tumor (10 of 49 patients), nodal disease (27 of 49 patients), and extracapsular spread (found in 12 of 27 patients with nodal disease) were all associated with poorer DSS ($p = .001$, .047, and .004, respectively) and OS ($p = .001$, .005, and .005, respectively). No statistically significant difference was seen between those who were positive versus those who were negative for EGFR expression. However, patients with a score of 4 had a trend toward both earlier disease-related events and poorer 5-year DSS (Figure 6). After multivariable regression with perineural invasion, nodal disease, extracapsular spread, and the biomarkers, the clinical covariates remained statistically significant predictors of survival.

DISCUSSION

The purpose of this study was to characterize the expression of 2 biomarkers, p16 and EGFR, in 2 separate cohorts of surgically treated patients: the first, patients with oropharyngeal SCC, and the second, patients with oral cavity SCC. For patients with oropharyngeal SCC, the results of this study demonstrate a distinct survival advantage for those with high levels of p16 expression and a survival disadvantage for those with high levels of EGFR expression. As combined markers, p16 and EGFR identified, with more accuracy, those patients with the best and worst survival. Several studies in the literature have demonstrated the importance of both p16 and EGFR in predicting survival of patients with oropharyngeal SCC; however, most are based on treatment with primary radiotherapy and cisplatin-based chemotherapy.[2,3,6–13] This study is unique in that it evaluates the predictive power of these 2 biomarkers in 2 surgically treated cohorts of patients with oropharyngeal SCC and shows

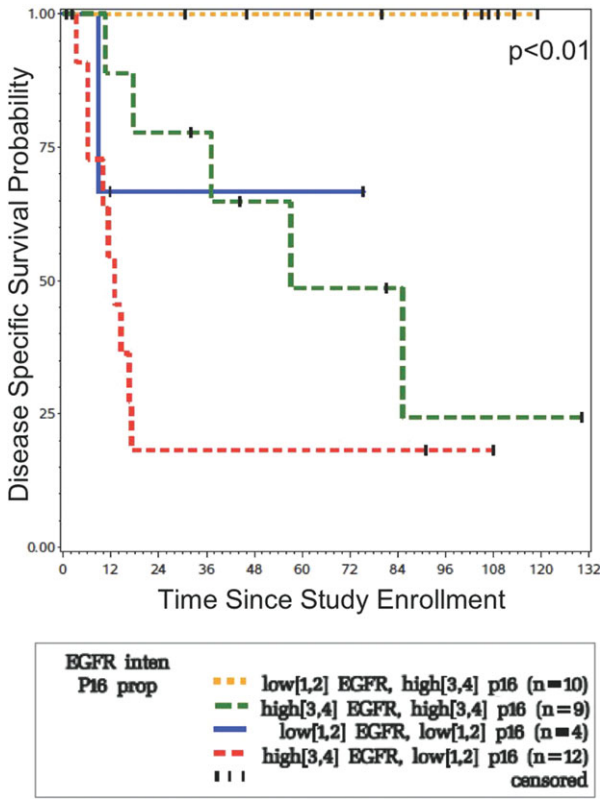

FIGURE 4. Disease-specific survival (DSS) of patients with oropharyngeal squamous cell carcinoma (SCC) according to combined epidermal growth factor receptor (EGFR) intensity and p16 proportion. Those with low EGFR/high p16 have the best DSS, whereas those with high EGFR/low p16 have the worst DSS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that p16 and EGFR are predictive in surgically treated patients. Furthermore, the patients with oropharyngeal SCC included in this study were treated at a time when surgery was the standard treatment for oropharyngeal SCC at the University of Michigan.

The p16 expression assessed through immunohistochemistry has now been accepted as a reliable biomarker for the HPV E7 oncoprotein,[12] thus acting as a surrogate marker for high-risk HPV infection in oropharyngeal SCC.[1,2,11,14,15] A previous study at the University of Michigan has demonstrated a very strong association between p16 and HPV copy number ($p < .001$).[2] Further, the importance of p16 expression may extend beyond that of being a surrogate marker of HPV infection. Lassen et al[11] argue that p16 positivity may identify HPV infections in oropharyngeal SCC that are transcriptionally active and thus may predict patient outcome more accurately than HPV detection.

A few studies have explored the role of HPV in surgically treated patients with oropharyngeal SCC.[16] Licitra et al[17] performed a retrospective review of 90 consecutive patients with oropharyngeal SCC, all treated with surgery +/− radiotherapy. Patients were evaluated for HPV DNA type 16 and 18, in association with a second biomarker, TP53. Multivariable regression analysis demonstrated that those tumors that were both HPV positive and contained wild-type TP53 had significantly improved survival. Ukpo et al[18] performed a retrospective review of 102 patients with oropharyngeal SCC, treated with surgery +/− radiotherapy. This study did not demonstrate any association between HPV status and survival. Conversely, Rich et al[15] performed a retrospective analysis of patients treated with transoral laser microsurgery ± adjuvant therapy. Increased expression of p16, assessed in tumors from 73 patients, was associated with improved survival. Interestingly, however, patients with positive HPV DNA (determined by in situ hybridization techniques) did not have significantly improved survival. Similar to our study, the majority of patients in this study (93%) received adjuvant radiotherapy. In our study, those patients with oropharyngeal SCC who had high levels of p16 expression had over 50% improved DSS in comparison with those with low levels of p16 expression at 5 years of follow-up. Although the biologic basis for the survival advantage conferred by p16 upregulation is unknown, a plausible explanation that prevails in the literature is that tumors expressing p16 are less hypoxic and, therefore, respond with less accelerated repopulation when irradiated, thus making them more susceptible to

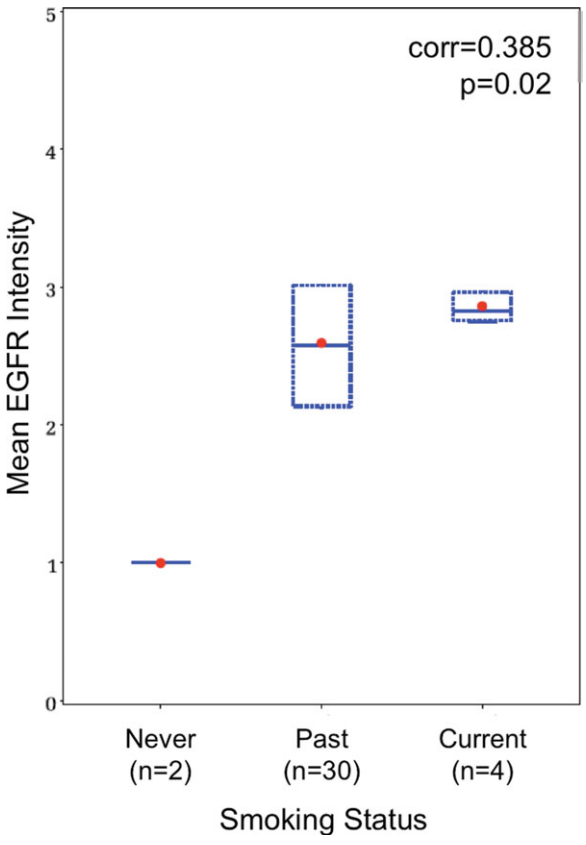

FIGURE 5. Correlation of mean epidermal growth factor receptor (EGFR) intensity with smoking status in patients with oropharyngeal squamous cell carcinoma (SCC). Higher levels of EGFR expression were associated with either past or current smoking status ($r = 0.385$; $p = .02$) Dot, mean; box, 25th to 75th percentile; horizontal bar, median; corr, Spearman correlation coefficient. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

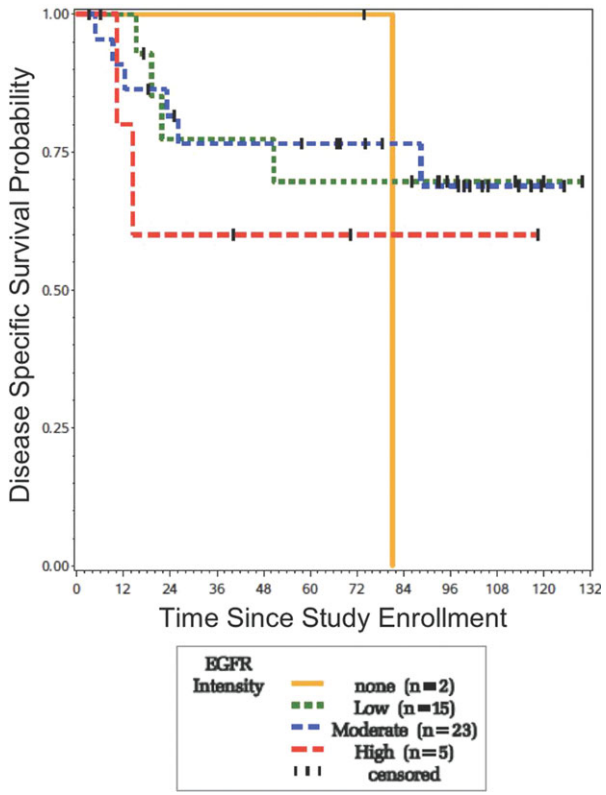

FIGURE 6. Survival of patients with oral cavity squamous cell carcinoma (SCC) according to epidermal growth factor receptor (EGFR) intensity. Those with the highest expression of EGFR have a trend toward poorer survival compared with those with none, low, or moderate staining. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

radiation.[11] The prevalence of p16 positivity in a large series evaluating patients with oropharyngeal SCC treated with conventional chemoradiation ranges from 19% to 95%.[3,7,9–11,14–16,18,19] Although this range is quite large, studies that evaluate the prevalence more recently tend to have a higher rate, suggesting an increase in the prevalence over time. The prevalence in our study (57%) is consistent with the studies that have assembled patient cohorts from a similar time period.

The prevalence of HPV in oral cavity SCC is not well established, but a few studies quote a range from 3% to 12%.[9,20] Our study demonstrated a p16 prevalence of 13%, in keeping with studies in the literature. P16 is much less likely to be a surrogate marker for HPV status in the oral cavity and, due to the low prevalence of p16 in our oral cavity SCC cohort, a survival analysis stratifying patients by p16 status was not feasible.

The role of EGFR expression in predicting the outcome for surgically treated patients with oropharyngeal SCC has yet to be elucidated. Preuss et al[4] conducted a retrospective case series of patients with oropharyngeal SCC treated with surgery ± radiotherapy and found no relation between EGFR expression and survival. Many studies, however, have demonstrated the relationship between EGFR expression and poorer survival in patients treated with primary chemoradiotherapy.[3,5,6,8,13,21] Further, the majority of patients in these studies demonstrate locoregional treatment failure, suggesting that tumors with high EGFR intensity may be radioresistant. In this surgical cohort, patients with high levels of EGFR expression also experienced poorer survival but the pattern of recurrence was different. The majority of patients treated surgically failed distantly, suggesting that surgery may result in better local/regional control but still requires an additional modality to address distant disease.

Most studies evaluating the role of EGFR expression in oral cavity SCC combine oral cavity SCC with other subsites of the head and neck.[6,8,13,21] One study that looked solely at oral cavity SCC found no association between EGFR expression and survival.[22] Our study suggests that patients with the highest score of EGFR intensity were associated with worsened survival and shorter time to recurrence when compared with those with lower EGFR intensity scores. This is consistent with our findings in the oropharyngeal SCC cohort. A study with a larger sample size may be able to demonstrate a statistically significant difference in survival in the oral cavity SCC cohort. Further, using a higher cut-point for the score that establishes EGFR positivity may also strengthen the ability to detect a difference with respect to survival.

Consistent with a small number of studies in the literature, EGFR expression was associated with smoking status in patients with oropharyngeal SCC.[2,23,24] However, smoking status was not an independent risk factor for worsened survival in this study. The analysis was hampered by a low frequency of patients with no smoking history. This study also suggested that both ECS and perivascular invasion, when considered alone, were negative prognosticators for those with oropharyngeal SCC. One of the mechanisms in which EGFR expression translates into advanced local/regional disease is through angiolymphatic invasion.[25] In this study, the addition of EGFR status to the survival model showed that EGFR expression was more predictive of survival than extracapsular extension and perivascular invasion, perhaps suggesting that EGFR may represent a range of invasive behaviors that encompass nodal metastasis, ECS, and perivascular invasion.

This study found that high p16/low EGFR expression was associated with improved survival in an oropharyngeal SCC surgical cohort, whereas these markers were not useful for prediction in patients with oral cavity SCC. The use of a combination of p16 and EGFR expression to predict survival in oropharyngeal SCC has only been reported in patients treated with primary chemoradiotherapy.[2,3] Based on the results of this study, we recommend that the patient with oropharyngeal SCC should have the primary tumor stained for both EGFR and p16 regardless of treatment modality.

CONCLUSION

This study suggests that in a surgically treated cohort of patients with oropharyngeal SCC, increased p16 expression predicts improved survival whereas increased EGFR expression predicts poorer survival. Used in combination, the 2 biomarkers may identify those who are likely to do well with treatment versus those who will do poorly. In addition, the prevalence of p16 differs significantly between the oral cavity and oropharynx subsites, whereas the prevalence of EGFR is similar between the 2

sites. For oral cavity SCC, clinical nodal status, ECS, and perineural invasion remain more important markers of prognosis than p16 or EGFR.

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