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ORIGINAL RESEARCH

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Treatment failure patterns are similar between p16− and p16+ oropharyngeal squamous cell carcinomas

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Abstract

Background: The incidence of p16+ oropharyngeal squamous cell carcinoma (OPSCC) has been increasing. The notion that p16+ OPSCC has a propensity for atypical and disseminating metastasis has gained traction. We compared treatment failure patterns in p16+ and p16− OPSCC and evaluated survival impact.

Methods: Retrospective analysis of patients with recurrent/metastatic OPSCC disease between 1/2009 and 12/2019.

Results: Thirty-eight p16+ and 36 p16− patients were identified. Three distinct failure patterns (distant vs. locoregional, atypical vs. typical, and disseminating vs. non-disseminating) were studied. No significant differences were found between p16+ and p16− patients. Multivariate analysis showed p16 status was an independent prognostic biomarker; p16+ patients have a favorable overall survival compared to p16− patients (HR 0.34, 95% CI 0.16–0.77; $P = .005$).

Conclusions: We challenge the view that p16+ OPSCC exhibits a distinctive treatment failure pattern and showed that p16 status impacts patient survival independent of disease progression.

KEYWORDS
disease progression, head and neck cancer, oropharyngeal cancer, p16, treatment failure

1 | INTRODUCTION

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been rising steadily in recent years. This is largely due to an increase in human papillomavirus-related (p16+) oropharyngeal disease, which now accounts for a majority of OPSCCs.[1] Widely recognized as a separate disease entity, p16+ OPSCC is distinguished by its etiology, pathophysiology, and clinical features. In contrast to p16− patients, those with p16+ OPSCC tend to have lower cumulative tobacco exposure and smaller primary tumors at diagnosis.[2] Although p16+ OPSCC is driven by viral oncoproteins, which promote the

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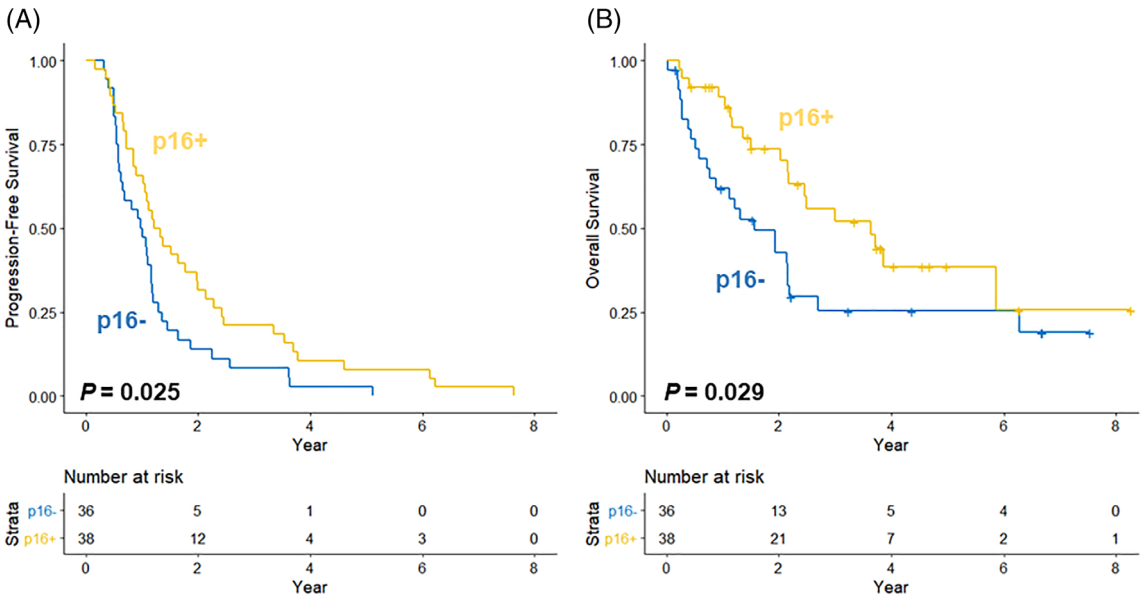

FIGURE 1 p16 status is a prognostic biomarker in treatment failure OPSCC patients. (A) Kaplan–Meier plot for PFS in p16+ and p16− treatment failure OPSCC patients. $P = .025$, log-rank. (B) Kaplan–Meier plot for OS in p16+ and p16− treatment failure OPSCC patients. $P = .029$, log-rank

TABLE 1 Treatment failure patterns in p16+ and p16− OPSCC

Treatment failure patterns	p16+ ($n = 38$) No. (%)	p16− ($n = 36$) No. (%)	*p*-value
Locoregional	20 (53)	22 (61)	.462
Distant	18 (47)	14 (39)	
Typical	31 (82)	28 (74)	.684
Atypical	7 (18)	8 (26)	
Nondisseminating	30 (79)	32 (84)	.246
Disseminating	8 (21)	4 (16)	

TABLE 2 Atypical failure sites in p16+ and p16− OPSCC

p16+	p16−
Abdominal wall	Axillary nodes
Brain	Pericardium
Cavernous sinus	Peritoneum
Pericardium	Skin
Periportal lymph node	Spleen
Skull base	
Sternoclavicular joint	

degradation of key tumor suppressor proteins p53 and Rb, p16− OPSCC is associated with tobacco use and is characterized by gain-of-function p53 mutations. Consequently, the molecular signatures and genomic profiles differ markedly between these two cancer types.[3–6]

Given the major differences in their tumor biology, p16+ and p16− OPSCC unsurprisingly show divergent clinical courses. After controlling for relevant clinical parameters such as age and tumor stage, p16+ patients show superior response to either chemoradiation or surgery.[2] For most of these patients, excellent locoregional control is achievable; however, a subset of p16+ OPSCC patients still experience disease progression. Several reports have suggested that p16+ OPSCC may exhibit a distinct pattern of distant metastasis.[7–9] Three main features: temporal delay in distant metastasis, propensity for dissemination defined as metastasis involving more than two anatomic sites, and involvement of atypical anatomic sites, have been described; although, these associations remain to be fully vetted. Moreover, the impact of these modes of treatment failure on OPSCC patient outcomes remains to be established.

Here, we report the findings of our own retrospective analysis of OPSCC patients who received treatment with curative intent at our academic medical center over the course of an 11-year period. Our study aimed to investigate treatment failure patterns in p16+ and p16− OPSCC patients, with a focus on the prognostic impact of these three modes of disease progression on overall survival (OS) following treatment failure.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

Our study (IRB# 20191051) was approved by our Institutional Review Board at University Hospitals Cleveland Medical Center. We queried our head and neck cancer clinical database and identified all

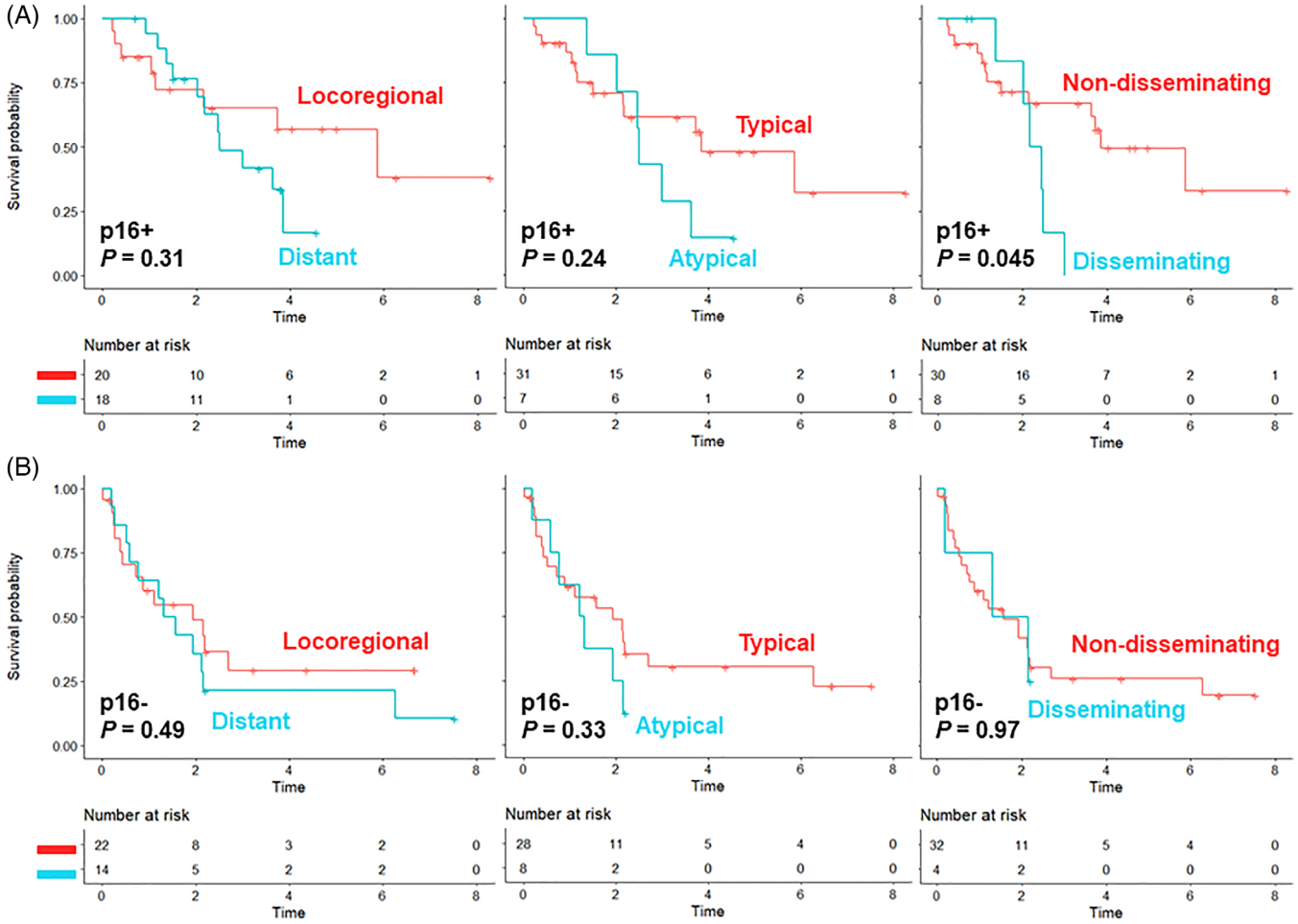

FIGURE 2 Treatment failure patterns and OS in p16+ and p16− OPSCC. (A) Kaplan–Meier plots for p16+ R/M OPSCC patients who presented with: locoregional and distant failures. $P = .31$, log-rank; atypical and typical failures. $P = .24$, log-rank; disseminating and nondisseminating failures. $P = .045$, log-rank. (B) Kaplan–Meier plots for p16− R/M OPSCC patients who presented with: locoregional and distant failures. $P = .49$, log-rank; atypical and typical failures. $P = .033$, log-rank; disseminating and non-disseminating failures. $P = .97$, log-rank

OPSCC patients treated between January 2009 and December 2019 at University Hospitals Seidman Cancer Center. This patient list was further reviewed and filtered, and included only OPSCC patients initially diagnosed with TxNxM0 disease with no previous history of other carcinomas. Treatment failure was defined as persistent or recurrent disease following or during treatment with curative intent. Atypical metastatic pattern was defined as any anatomical site other than lung, liver, or bone and disseminating metastatic pattern was defined as distant metastases in greater than two organ systems. Tobacco smoking status was defined as yes, if a patient self-identified as a current/former smoker at initial diagnosis or no if a patient had no smoking history. p16 IHC is a standard of care assay for OPSCC at our academic medical center and defined as p16+, if there was strong and diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells.

2.2 | Statistical analysis

All statistical analyses were performed using R (version 4.0.2). Log-rank testing was performed for each group-wise comparison. Categorical variables were summarized using frequencies and compared using Fisher's exact test for 2 × 2 contingency tables. Progression-free survival (PFS; time of diagnosis to time of treatment failure) and OS (time of treatment failure to time of death or last follow-up) analyses were performed with Kaplan–Meier curves and log-rank tests using the R packages *survival* and *ggplot2*. Multivariate proportion hazards regression analysis was utilized to create a forest plot. $P < .05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Treatment failure patterns in p16+ and p16− OPSCC

We reviewed 376 patients diagnosed with TxNxM0 OPSCC with no previous history of other malignancies. Treatment failure rate was higher in p16− (32.7%; 36/110) than in p16+ (14.3%; 38/266) OPSCC patients ($P < .001$, X^2). As shown in Figure 1A, p16− OPSCC

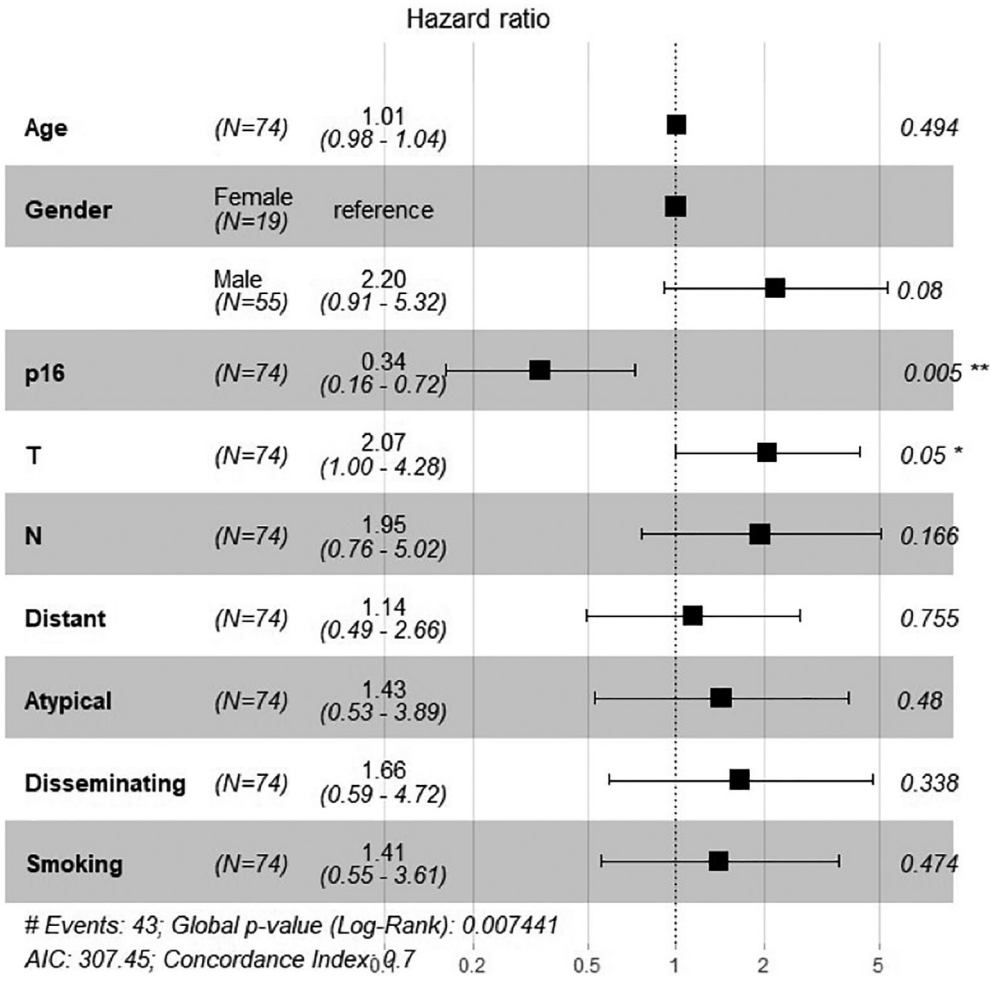

FIGURE 3 p16 status is an independent prognostic biomarker in treatment failure OPSCC patients. Multivariate regression model presented as a forest plot. T (clinical T stage; T1/2 vs. T3/4). N (nodal status; N− vs. N+). Distant (locoregional vs. distant metastasis). Atypical (typical vs. atypical failure pattern). Disseminating (nondisseminating vs. disseminating failure pattern). Smoking (yes or no)

patients tend to fail treatment earlier than p16+ OPSCC patients; median PFS was 0.98 and 1.22 years for p16− and p16+ patients, respectively ($P = .025$, log-rank). We assessed three modes of treatment failure, distant versus locoregional, atypical versus typical, and disseminating versus nondisseminating, and did not find a significant difference in these patterns between p16+ and p16− OPSCC patients (Table 1). Overlapping and distinct atypical failure sites were observed between p16+ and p16− OPSCC (Table 2).

3.2 | p16 is an independent prognostic biomarker in R/M OPSCC

p16+ status is well recognized as a favorable biomarker for OS in OPSCC.[2,10] Analysis of our defined R/M OPSCC cohort is consistent with published data and showed that p16+ patients have superior OS compared to p16− patients ($P = .029$, log-rank; Figure 1B). Median OS was 3.31 years for p16+ patients and 1.57 years for p16− patients.

Next, we examined the impact of these three treatment failure patterns on OS (Figure 2). p16+ patients tend to have better OS than p16− patients in all three-treatment failure patterns analyzed. In p16− and p16+ OPSCC, locoregional failures patients had similar OS compared to distant failure patients. Patients presented with typical and atypical sites of failure did not have disparate clinical outcomes regardless of p16 status. We found that p16+ patients with nondisseminating metastasis had superior OS compared to disseminating metastatic p16+ patients; median OS of 3.85 and 2.17 years for nondisseminating and disseminating disease, respectively ($P = .045$, log-rank).

As shown in Figure 3, multivariate Cox models, adjusting for p16 and other co-variates, including modes of treatment failure, showed that p16 status conferred favorable prognosis and remained a significant prognostic biomarker (HR 0.34, 95% CI 0.16–0.72; $P = .005$). In addition to p16 status, clinical T stage was found to be an independent prognostic biomarker. T3/4 OPSCC patients had a 2.07-fold increase ($P = .05$) in risk of death compared to T1/2 patients. Other co-variates, age, gender, nodal status (N+ vs. N−), smoking, distant metastasis (locoregional vs. distant), atypical metastatic disease (typical vs. atypical), and disseminating phenotype (nondisseminating vs. disseminating) were not independent prognostic factors.

4 | DISCUSSION

There is a perception in our field that p16+ OPSCC patients have a distinct failure pattern compared to p16− OPSCC patients. This

notion is primarily driven by the first published study in this space by Huang et al. from the University of Toronto.[7] The Toronto group analyzed data from a cohort of 36 patients and reported that metastasis to multiple anatomic sites occurred in 46% of p16+ patients compared to none of their p16− patients ($P = .005$). Additionally, they described a tendency for p16+ OPSCC patients to metastasize to various atypical sites including the brain and nonregional lymph nodes, whereas no unusual sites of involvement were noted for p16− patients.

Some of the conclusions reached by Huang et al. have been, subsequently, corroborated by another study, whereas other groups reported conflicting data. Jaber et al. showed that 74% (44/59) of p16+ patients had metastases involving more than one distant anatomic site compared to 10% (3/30) of p16− patients ($P < .001$).[9] However, three independent groups, Trosman et al., Sinha et al., and Guo et al. reported that the metastatic disease dissemination pattern did not differ significantly between their p16+ and p16− OPSCC patients.[8,11,12] A greater number of atypical sites in p16+ patients was described by Jaber et al. and Trosman et al., however, some atypical metastases were also identified in p16− patients.[8,11] Although these two studies are in line with data from Huang et al. in describing a trend for an atypical metastatic pattern in p16+ OPSCC patients, none performed the required analysis to demonstrate a statistically significant difference between the p16+ and p16− groups.[7–9] It is important to note that in each of these studies, the p16+ patients outnumber their p16− counterparts by a large margin, so a greater number of atypical sites is expected in the p16+ groups. In contrast, based on appropriate statistical analysis, Sinha et al. reported that the distribution of metastasis to particular anatomic sites, atypical versus typical, between p16+ and p16− patients was not statistically different.[11]

Our study investigated failure patterns in OPSCC patients treated at our institution over an 11-year period. We identified 74 OPSCC patients who failed definitive treatment; 38 p16+ and 36 p16− cases. After stratifying our OPSCC cohort by p16 status, no statistically significant interactions were observed between p16 status and any treatment failure pattern we examined: locoregional versus distant ($P = .462$), typical versus atypical metastatic site ($P = .684$), and nondisseminating versus disseminating ($P = .246$). Our study differed from most of the other reports in that we excluded patients with any past or current cancer diagnosis in addition to OPSCC. Sinha et al., whose findings were similar to our own, excluded patients with a past history of HNSCC; however exclusion of patients with other cancer types was not specifically mentioned.[11] Interestingly, Huang et al. reported that a considerable number of patients in their study (12.9%) had previous cancer diagnoses.[7] Of the patients with a previous history of other carcinomas, p16+ patients tend to have a higher proportion of non-HNSCC malignancies, which could drive a non-HNSCC pattern of metastatic spread.[7] Therefore, atypical metastatic lesions described in their OPSCC patients may be a consequence of their previously diagnosed malignancies, such as breast and lung cancers. Without histologic confirmation of metastatic deposits in these patients, it is impossible to conclusively establish the primary tumor responsible for the metastatic lesion. Based on these arguments, the exclusion of patients with other cancer diagnoses is a necessary consideration to ensure that the observed metastatic behavior is directly attributable to the OPSCC primary tumor. Studies, which do not filter out OPSCC patients with a previous history of other malignancies, such as Huang et al., Trosman et al., and Jaber et al.[7,8,11] need to be interpreted with extreme caution.

Regardless of the relative frequencies of these failure patterns in p16+ and p16− OPSCC patients, the potential for each of these patterns to occur in either group is clear. There is a consensus that among OPSCC patients who experience treatment failure, those with p16+ disease have significantly longer survival.[7,8,10,11] However, the prognostic significance and treatment management considerations of treatment failure patterns in OPSCC have not been fully explored. Our results corroborate these earlier studies and provide further evidence that p16+ status is a favorable prognostic biomarker in the R/M OPSCC setting. Analyses to determine the clinical impact of treatment failure patterns illuminated one key point to highlight: in p16+ patients, nondisseminating disease is associated with better outcomes compared to disseminating disease. This finding suggests that the p16+ OPSCC patients who present with nondisseminating disease, which may include oligometastatic disease, should be managed with curative intent and should not be counseled toward palliative care for end-stage disease management.

Studies published on p16 status and treatment failure patterns, including our own, share some limitations. Since patients with p16+ OPSCC generally respond well to treatment, treatment failures—and unusual modes of treatment failure, in particular—are relatively uncommon. For most single institution cohort studies, the number of failure events may constrain statistical power to identify meaningful group differences. This reality may divide opinion on the most appropriate interpretation of apparent trends when statistical significance is lacking. Certainly, meaningful differences can occur without statistical significance but these are difficult to confidently distinguish from random variation. Although the view that p16+ OPSCC has a propensity to involve atypical metastatic sites has been endorsed by several groups and has gained traction, to the best of our knowledge, statistically significant differences in site distribution have not been reported. We took a pragmatic approach and drew our conclusions based on statistical analysis. Our analyses in an appropriately defined OPSCC cohort, TxNxM0 without a previous history of other malignancies, showed that treatment failure patterns, atypical versus typical and disseminating versus nondisseminating, are similar between p16+ and p16− OPSCC.

Although many questions remain, a couple of points are well-established: distant metastasis, atypical metastatic sites, and dissemination occur infrequently in both p16+ and p16− OPSCC patients, and p16+ and p16− OPSCC are biologically and clinically distinct diseases. Given these facts, we question the clinical utility of continuing to compare failure patterns between these two diseases and argue that future research should instead focus on the clinical significance and management considerations related to failure events within each patient group.

CONFLICT OF INTEREST

None reported.

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