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Characterizing distant metastases and survival in oropharyngeal squamous cell carcinoma

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Abstract

Background: Outcomes of oropharyngeal squamous cell carcinoma (OPSCC) after development of distant metastases (DM) in the context of human papillomavirus (HPV) tumor status remain controversial in the literature.

Methods: OPSCC patients with DM treated between June 2015 and March 2019 were included from a prospectively enrolled database. Characteristics of DM including sites, episodes, and timing of disease were analyzed in addition to survival after DM.

Results: Sixty-nine HPV-positive and 18 HPV-negative OPSCC patients with DM were included. The 2-year survival after DM was higher for HPV-positive patients (54.0% vs. 11.3%, $p < 0.001$). HPV-positive patients did not demonstrate greater episodes or sites of DM. Multiple sites of DM, early development of DM, and Charlson comorbidity Index were independently associated with worse survival after DM.

Conclusions: While multiple sites, early DM, and comorbidities were poor prognostic factors, OPSCC patients with distant progression can have substantial survival after DM, including M1 patients.

KEYWORDS

distant metastases, HPV, OPSCC, oropharyngeal squamous cell carcinoma, p16

1 | INTRODUCTION

The incidence of human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has continued to rise over the past decade and accounts for the majority of newly diagnosed oropharyngeal cancers.[1,2] While HPV-positive OPSCC has a significantly better prognosis and response to treatment, about 5%–

13% of patients will still develop distant metastases (DM) by 3 years.[1,2] Some prior reports have described the unique clinical behavior of distant disease in the setting of HPV-positive OPSCC, such as multi-organ metastases or "explosive metastases."[3,4] Increasing evidence has shown that HPV-positive tumors may be associated with late or delayed metastases, which may also be related to the long survival of these patients.[5-7]

The literature addressing whether HPV-positive patients demonstrate unique patterns of DM progression remains equivocal.[8] Huang et al found that while the DM

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rate was similar in both HPV-positive and HPV-negative patients, the HPV-positive DM were more likely to disseminate to multiple organs,[5] or "unusual sites" as reported in some smaller series.[4,7,9] These findings of unusual sites of DM have not been confirmed by other case studies,[10,11] and several studies have consistently reported the lungs as the most common site of DM regardless of HPV status.[2,5-7,9]

With regard to the timing of distant progression, HPV-positive DM have also been reported to occur later than HPV-negative DM with a longer median time to distant failure (16.4 vs. 7.2 months).[7] However, a secondary analysis of RTOG 0129 and 0522 did not identify differences in time to distant failure.[11] Survivorship bias may contribute to the apparent late distant failures in HPV-positive patients.[6,10] Despite these differing results, there is consensus in the literature that most DM occur within 3 years, regardless of HPV status.[1-3,8]

Within this context, we performed a review of distant metastatic disease from OPSCC treated at MD Anderson Cancer Center through a prospectively collected clinical cohort. Through this cohort, we sought to clarify how patterns of distant disease differ between HPV-positive and HPV-negative disease and identify factors related to survival after distant progression.

2 | MATERIALS AND METHODS

2.1 | Participants

Patients were identified from the IRB-approved Charles Stiefel Oropharyngeal Cancer Program, a prospectively collected clinical database from which patients treated at MD Anderson for OPSCC. Collection of additional clinical data was approved through an additional IRB protocol (Protocol #2019-1137) including treatment outcomes and recurrence. A total of 1459 OPSCC patients treated at MD Anderson Cancer Center between June 2015 and March 2019 were searched to identify patients that developed DM, which were then treated at MD Anderson Cancer Center. Only those with confirmed p16 and/or HPV tumor status were included. Additional clinical data were collected from medical chart abstraction included age, sex, smoking history, primary treatment modality, treatment modality of distant metastasis, date of distant metastatic diagnosis, time to first distant metastasis, and survival after DM. Patients were staged based on AJCC eighth edition TNM staging. Information about organ site of DM, episodes of DM, and comorbidities were also collected. Charlson Comorbidity Index was calculated from reported comorbidities.[12] Sites of DM were grouped by

organ site as: pulmonary, bone, liver, brain, and other soft tissues. An additional episode of distant metastasis was defined as a new organ site of metastasis diagnosed at a unique time point.

2.2 | Statistical analysis

Statistical analysis was conducted using Stata 14.1 (Stata Corp, LLC, College Station, TX, USA). Student's 2-tailed t-test was used for comparison of normally distributed means, and Wilcoxon rank sum for comparisons of medians. For comparison of categorical data, chi-squared tests were utilized for comparison, with the exception of variables with expected cell values <5 for which Fisher's exact test was utilized. Primary endpoint was overall survival after distant metastatic progression. Survival analyses were performed using Kaplan–Meier curves, with log rank testing used for comparison between groups. Cox proportional-hazards models were utilized for multicovariate analysis of survival after DM, excluding M1 patients.

3 | RESULTS

3.1 | Patient characteristics

Of 1459 OPSCC patients treated at MD Anderson Cancer Center between June 2015 and March 2019, 87 patients developed DM and were included in this study, with median follow-up of 14.7 months following distant metastatic progression for surviving patients. Table 1 summarizes patient demographics, further categorized by HPV tumor status. The majority of OPSCC patients were male (90.8%), HPV-positive (79.3%), and former smokers (55.2%). Consistent with the prior literature, HPV-positive patients were more likely to be male (95.7% vs. 72.2%, $p = 0.008$), never smokers (36.2% vs. 5.6%, $p < 0.001$), and less likely to experience locoregional recurrence (21.5% vs. 50%, $p = 0.017$) when compared to HPV-negative patients. Based on tumor classification using AJCC eighth edition, the majority of HPV-positive patients had T2-T3 primary disease (60.9%) at presentation, compared to HPV-negative patients who presented with lower T0-T1 primary disease (55.6%). Regarding nodal classification, the majority of patients who developed DM presented with nodal classification of N2b, N2c, or N3, regardless of HPV status. The average Charlson Comorbidity Index score was 6.3 in HPV-positive patients 7.3 in HPV-negative patients ($p = 0.04$). Notably, all patients had a minimum Charlson score of 6 due to the presence of solid metastases.

TABLE 1 Patient characteristics

	All (87 patients) (%)	HPV-positive (69 patients)	HPV-negative (18 patients)	p
Age at primary diagnosis (mean)	59.6	59.9	58.8	0.60
Sex				
Male	79 (90.8)	66 (95.7)	13 (72.2)	**0.008**
Female	8 (9.2)	3 (4.3)	5 (27.8)	
Tobacco				
Never	25 (28.7)	24 (36.2)	1 (5.6)	**<0.001**
Former	48 (55.2)	40 (58.0)	8 (44.4)	
Current	14 (16.1)	5 (7.2)	9 (50.0)	
Charlson score	6.5	6.3	7.3	0.04
Score < 7	79 (90.8)	66 (95.7)	13 (72.2)	
Score > 7	8 (9.2)	3 (4.3)	5 (27.8)	
Initial T classification (AJCC 8)				
T0	10 (11.8)	4 (6.0)	6 (33.3)	**0.009**
T1	18 (21.1)	14 (20.9)	4 (22.2)	
T2	31 (36.4)	28 (41.8)	3 (16.7)	
T3	13 (15.3)	12 (17.9)	1 (5.6)	
T4	13 (15.3)	9 (13.4)	4 (22.2)	
Initial N classification (AJCC 8)				
N0	3 (3.5)	3 (4.3)	0 (0.00)	0.96
N1	50 (58.8)	38 (56.7)	12 (66.7)	
N2	25 (29.4)	20 (29.9)	5 (27.8)	
N3	7 (8.2)	6 (9.0)	1 (5.6)	
Initial M classification				
M0	73 (83.9)	55 (79.7)	18 (100.0)	**0.036**
M1	14 (16.1)	14 (20.3)	0	
Median follow-up of surviving patients after DM (months)	14.7	14.7	13.4	0.702
Time to first DM[a] (median in months)	13.8	16.6	8.7	**0.006**
Number of DM episodes (mean)	1.40	1.42	1.33	0.69
Number of DM sites (mean)	1.62	1.67	1.44	0.34
Locoregional recurrence	23 (27.7)	14 (21.5)	9 (50)	**0.017**
Treatment of primary disease				
Surgery ± adjuvant therapy	6 (6.9)	4 (5.8)	2 (11.1)	0.564
Non-surgical treatment	81 (94.1)	65 (94.2)	16 (88.9)	
Treatment of M1 disease			n/a	
Induction + chemoradiation		7 (50)		
Chemoradiation + local therapy to DM		2 (14.3)		
Chemotherapy alone		5 (35.7)		
Treatment with immunotherapy				
For first DM episode	49 (56.3)	35 (50.7)	14 (77.8)	**0.039**
For any DM episode	56 (64.4)	42 (60.9)	14 (77.8)	0.182

[a]Excluding those with DM at presentation.

Abbreviations: DM, distant metastases; HPV, human papillomavirus.

3.2 | Treatment

3.2.1 | Primary treatment

Most (95.1%) patients who developed DM received non-surgical treatment for their initial treatment, regardless of HPV tumor status. Of the 61 patients who received chemotherapy, 52 patients had data available on concurrent agents used for primary treatment with 55.7% receiving cisplatin, 25.0% receiving carboplatin, and 19.2% receiving cetuximab.

Within this cohort, patients with M1 disease at presentation were all HPV-positive. For these patients, half received induction chemotherapy followed by definitive chemoradiation. In addition, two M1 patients received chemoradiation to the primary site and additional treatment to the metastatic site (one received surgery and one received stereotactic radiation). The remainder received systemic therapy alone. For the remainder of the analysis, M1 patients were excluded from the analysis.

3.2.2 | Immunotherapy for DM

Patients were also categorized by whether they received immunotherapy (checkpoint inhibitor-based therapy) for the first DM episode, or at any point during their treatment. The majority of patients were treated with immunotherapy at some point during their treatment (64.4%), but HPV-negative patients were more likely to receive immunotherapy for treatment of first DM episode.

3.3 | Characteristics of distant metastasis by HPV tumor status

3.3.1 | Organ sites and episodes

Sites of distant disease were reported based on metastases at each organ site at any time during the follow-up period. Sites of disease were compared by HPV tumor status (Table 2). Of all sites, pulmonary metastases (lung and mediastinum) were the most common (53.3%) with a higher incidence in HPV-positive patients on univariate analysis. The next most common sites of disease were bone (17.8%), liver (11.9%), brain (9.3%), and other soft tissue (7.6%), all of which did not differ significant based on HPV-status.

Regarding episodes of DM, or each independent time point for diagnosis of new DM, patients experienced a mean of 1.4 DM episodes, which did not differ based on HPV-status. The sites of DM were grouped by organ system (pulmonary, bone, liver, brain, and other soft tissue), and the mean number of sites per patient was 1.62 DM sites. Again, number of sites did not differ by HPV status.

3.3.2 | Time to distant metastasis

Median time to develop distant metastases from the time of diagnosis (excluding M1 patients with DM at presentation) was 13.8 months for all OPSCC patients, with HPV-positive patients showing a significantly longer median time to development of DM (16.6 vs 8.7 months). In Kaplan–Meier survival analysis, HPV-positive tumor status demonstrated a trend toward longer time to DM (Figure 1, $p = 0.079$). In HPV-negative patients who developed DM, a large majority (83.3%) develop DM within 1 year. In contrast, only 38.2% of HPV-positive patients developed DM within the first year. The 2- and 3-year cumulative incidence of DM was 74.6% and 89.1% for HPV-positive patients, respectively.

3.4 | Factors impacting survival after distant metastatic progression

HPV-positive tumor status was significantly associated with improved survival after development of DM (Figure 2, $p = 0.0003$). The 1-, 2-, and 3-year survival for HPV-positive patients was 74.2%, 45.3%, and 30.5%, respectively,

TABLE 2 Sites of distant metastasis

Location of DM	All (n = 73) (%)	HPV-positive (n = 55)	HPV-negative (n = 18)	p
Pulmonary (lung/mediastinum)	63 (53.3)	50 (54.4)	13 (72.2)	0.05
Bone	21 (17.8)	15 (16.3)	6 (33.3)	0.62
Liver	14 (11.9)	9 (9.8)	5 (27.8)	0.29
Brain	11 (9.3)	10 (10.9)	1 (5.6)	0.19
Other soft tissues (abdominal, dermal, muscle, adrenal, kidney)	9 (7.6)	8 (8.6)	1 (5.6)	0.31

Abbreviation: HPV, human papillomavirus.

compared to HPV-negative survival after DM with 1-, 2-, and 3-year survival of 37.5%, 11.3%, and 11.3%, respectively.

Treatment with immunotherapy was not significantly associated with improved survival after development of DM. Receipt of immunotherapy for the first episode of DM was not associated with survival after DM ($p = 0.998$), and this was true for both HPV-positive ($p = 0.448$) as well as HPV-negative patients ($p = 0.669$). Similarly, the receipt of immunotherapy at any point
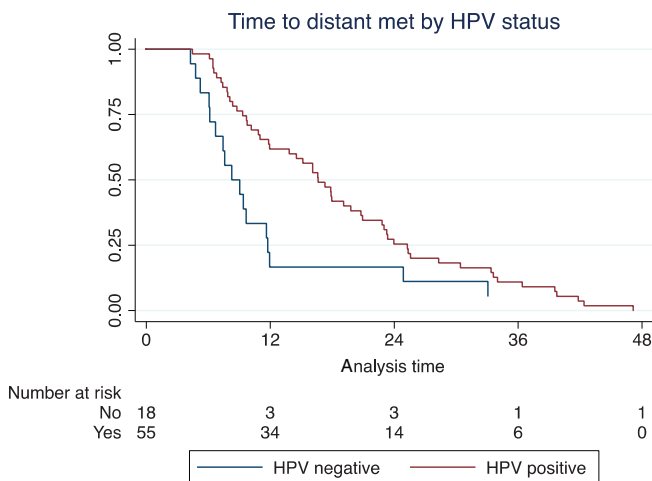

FIGURE 1 Kaplan–Meier estimates for time to distant metastases (DM) by human papillomavirus (HPV) status, excluding M1 disease ($p = 0.079$), an HPV-positive 1-year rate of DM-free survival of 61.8% and 2-year DM-free survival of 25.4% and an HPV-negative 1-year DM-free survival of 16.7% and 2-year DM-free survival of 16.7% [Color figure can be viewed at wileyonlinelibrary.com]
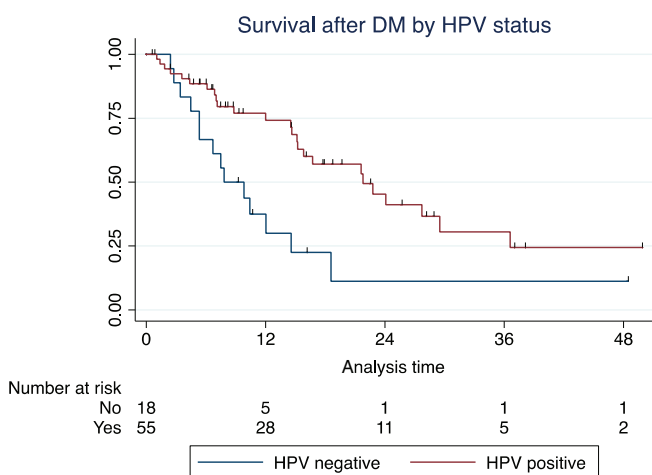
during treatment was not associated with survival after DM (0.824), and this did not differ by HPV tumor status.

3.4.1 | Time to first distant metastasis

Early development of distant metastasis or disease recurrence has been associated with more aggressive disease. To better characterize the effect of timing of DM, the cohort was divided into patients who developed early DM (<12 months) compared to late DM (≥12 months after initial diagnosis). Late metastasis was associated with a significant survival advantage (Figure 3, $p = 0.0019$). Two-year survival after development of metastases for patients with early DM was 19.3% compared to 57.7% for those with late DM.

In contrast to the survival advantage of those with late DM, patients who presented with M1 disease (not included in the prior analysis) had improved 2-year survival after DM compared to those with M0 disease at diagnosis. Survival after DM was significantly improved in the whole cohort ($p = 0.012$) as well as when restricting analysis to HPV-positive patients ($p = 0.046$), given that all M1 patients were HPV-positive. For HPV-positive patients, M1 patients experienced a 2-year survival after DM of 82.5% versus 45.3% for M0 patients (Figure 4).

3.4.2 | Site of distant metastasis

HPV-positive patients were more likely to have metastases to the lungs/mediastinum ($p = 0.05$) though the

FIGURE 2 Kaplan–Meier estimates for survival after distant metastases by human papillomavirus (HPV) status ($p = 0.0003$), with an HPV-positive 1-year survival of 74.2% and 2-year survival of 45.3% versus an HPV-negative 1-year survival of 37.5% and 2-year survival of 11.3% [Color figure can be viewed at wileyonlinelibrary.com]
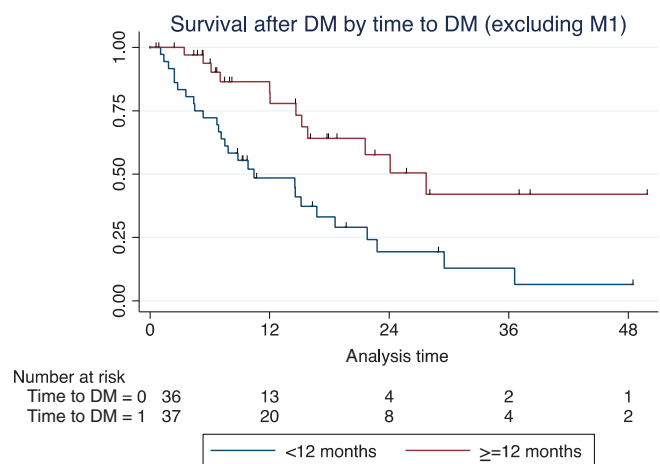

FIGURE 3 Kaplan–Meier estimates for survival after distant metastases (DM) by time to DM (excluding M1) ($p = 0.0019$), with an early DM 1-year survival of 48.5% and 2-year survival of 19.3% versus a late DM 1-year survival of 82.2% and 2-year survival of 57.7% [Color figure can be viewed at wileyonlinelibrary.com]
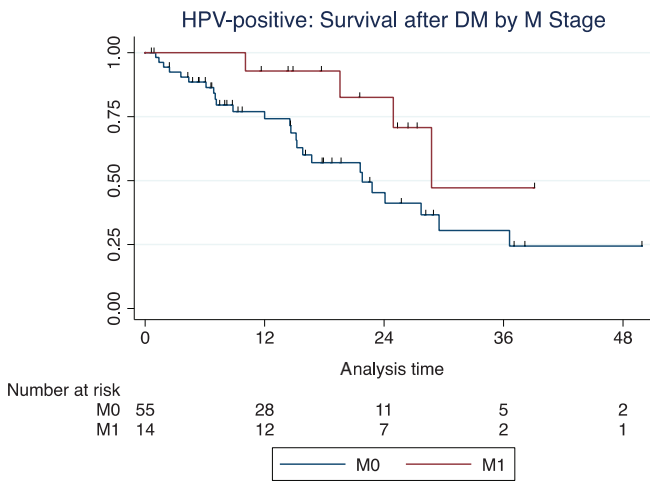
FIGURE 4 Kaplan–Meier estimates for survival after distant metastases by M stage ($p = 0.046$), with an M0 1-year survival of 74.2% and 2-year survival of 45.3% versus an M1 1-year survival of 92.9% and 2-year survival of 82.5% survival [Color figure can be viewed at wileyonlinelibrary.com]

lungs/mediastinum were the most common site of metastases regardless of HPV-status. (Table 2). Patients with single organ DM demonstrated a clear survival advantage (Figure 5(A), $p = 0.011$) when compared to those with multiple sites of DM. In contrast, survival did not differ for patients with single vs multiple episodes of DM (Figure 5(B), $p = 0.160$). In the context of additional disease sites, the survival for patients who also experienced any locoregional recurrence during their disease course was significantly worse (Figure 5(C), $p = 0.0035$). DM to bone were associated with worse survival ($p = 0.0257$) and patients with pulmonary metastasis showed a trend toward improved survival ($p = 0.055$) ($p = 0.12$, Figure S1). A separate Kaplan–Meier analysis including patients with M1 disease showed a survival advantage for M1 patients with a 2-year survival of 82.5% versus 45.3% in M0 patients.

3.4.3 | Cox multi-covariate analysis

Overall survival after development of DM was then evaluated within a Cox proportional hazards model (Table 3). In univariate analysis, HPV-positive tumor status (hazard ratio (HR) 0.392, $p = 0.006$) and late DM, ≥ 12 months from primary diagnosis to first DM (HR 0.355, $p = 0.003$), were associated with improved survival after DM. Involvement of multiple organ sites (HR 2.293, $p = 0.013$) and presence of locoregional recurrence (HR 2.538, $p = 0.005$) were associated with decreased survival after DM, and high Charlson score also showed trend toward worse survival after DM (HR 2.615, $p = 0.054$). In the multi-covariate model, both
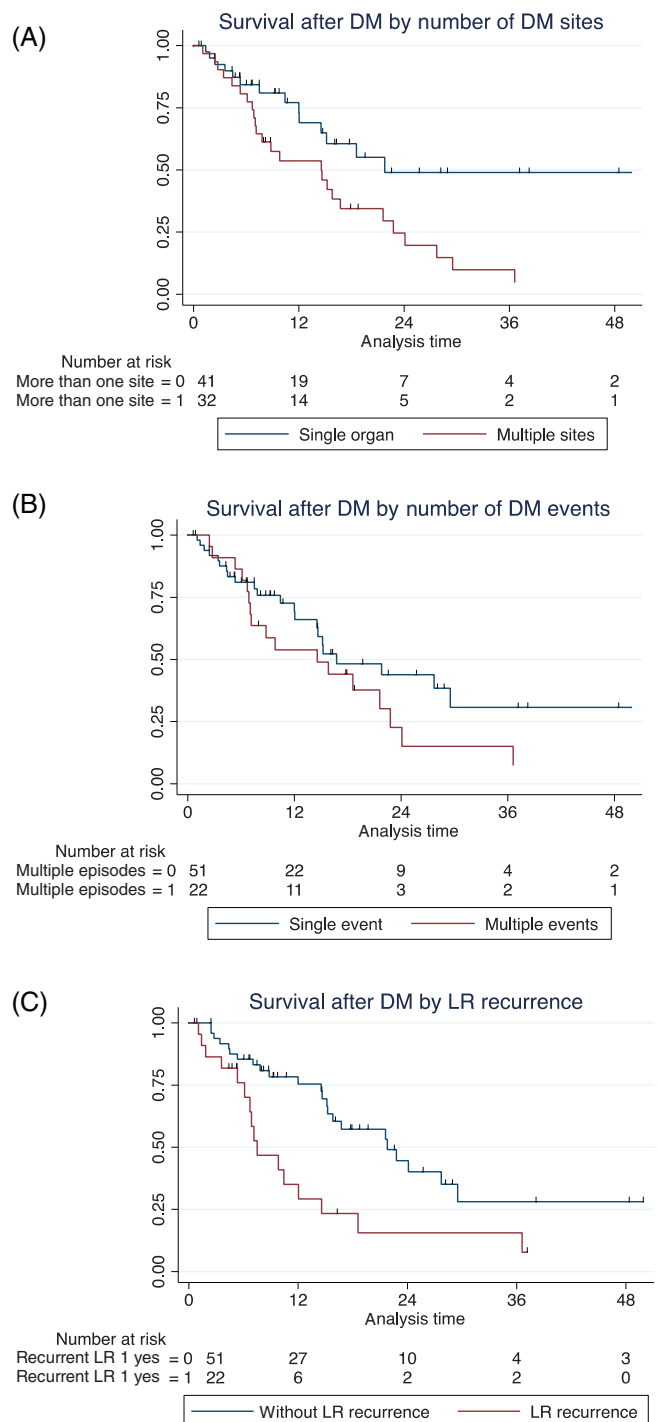

(A)

(B)

(C)

FIGURE 5 (A) Kaplan–Meier estimates for survival after distant metastases (DM) by number of sites of DM ($p = 0.011$), with a single organ DM 1-year survival of 73.0% and 2-year survival of 49.0% versus a multi-organ DM 1-year survival of 53.6% and 2-year survival of 24.6% (B) Kaplan–Meier estimates for survival after DM by number of DM events ($p = 0.160$), with a single DM event 1-year survival of 69.3% and 2-year survival of 43.9% versus a multiple DM-event 1-year survival of 53.9% and 2-year survival of 22.7% and (C) Kaplan–Meier estimates for survival after DM by LR ($p = 0.0035$), with no LR recurrence alongside DM 1-year survival of 75.4% and 2-year survival of 44.6% versus LR recurrence alongside DM 1-year survival of 35.1% and 2-year survival of 15.6% [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Survival after distant metastases (DM) (excludes M1) Cox proportional hazards model

Variable	Univariate model			Multi-covariate model		
	HR	p	95% CI	HR	p	95% CI
Age	0.985	0.440	0.945–1.03	-		
Current smoker	1.266	0.575	0.555–2.88	-		
HPV positive	**0.392**	**0.006**	**0.200–0.768**	-		
Multiple episodes	1.570	0.164	0.832–2.963	-		
Multiple sites of DM	**2.293**	**0.013**	**1.191–4.416**	2.356	0.011	1.217–4.560
Late (≥12 months) versus early (<12 months) DM	**0.355**	**0.003**	**0.179–0.702**	0.387	0.008	0.193–0.776
LR recurrence	**2.538**	**0.005**	**1.328–4.850**	-		
Charlson score	**1.420**	**0.011**	**1.083–1.861**	1.381	0.025	1.041–1.831

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; LR, locoregional.

DM to multiple sites (adjusted HR (aHR) 2.356, 95% confidence interval (CI) 1.217–4.560, $p = 0.011$) and Charlson comorbidity score (aHR 1.381, 95% CI 1.041–1.831, $p = 0.025$) were independently associated with increased risk of death after DM.. Conversely, patients with late DM were associated with decreased risk of death (aHR 0.387, 95% CI 0.193–0.776, $p = 0.008$). Other variables including HPV status, age, smoking history, multiple episodes of DM, and locoregional recurrence were not independently associated with survival after development of DM.

4 | DISCUSSION

The findings from this study add to the current literature characterizing the patterns of distant disease in the context of HPV tumor status, showing HPV-positive status was associated with significantly improved survival after development of DM, but not association with greater sites of disease nor greater number of DM episodes. Consistent with previously published literature, there was a clear survival advantage associated with HPV-positive tumor status, with 2-year survival of 77.3% compared to 39.9% for HPV-negative patients.[1] It is well-established that the lungs are the most common site of DM as found in this study, and there was not a clear propensity for multiorgan disease in HPV-positive patients in our study cohort. We also found that number of DM episodes during patients' disease course did not differ between HPV-positive and HPV-negative patients, and HPV-positive patients did not exhibit "explosive metastases" compared to in HPV-negative patients.[5,13]

In this study, patients with HPV-positive OPSCC had a 2-year survival after DM of 45.3% compared to HPV-negative patients with 11.3% 2-year survival. Historically, similar studies have reported significantly lower survival following distant progression in both HPV positive and HPV negative OPSCC patients. In a 2013 study mainly examining patients treated non-surgically, Huang et al found a 2-year survival of 11% and 4% for HPV-positive patients and HPV-negative patients respectively after DM.[5] Similarly in a study including patients treated both surgically and non-surgically, Sinha et al reported a 3-year disease-specific survival of 16% for p16-positive patients, and 0% in p16-negative patients.[8] A more contemporary study from 2015 reported better outcomes in a small cohort of 37 patients with median OS after distant failure of 25.6 months in HPV-positive patients and 11.1 months in HPV negative, similar to our cohort (24.1 months HPV-positive and 7.8 months HPV-negative, Figure 2).[7] Similarly, 2020 retrospective analysis of the NCDB including 768 patients with M1 OPSCC disease showed a 2-year OS of 42% in HPV-positive patients with DM and 28% in HPV-negative patients.

These improved survival outcomes after DM in OPSCC seen in this study and more recent publications could be attributed to specific patient populations treated at a quaternary care center, access to early phase clinical trials for treatment of metastatic disease, or the addition of immunotherapy to treatment regimens. In 2016, pembrolizumab was FDA approved for treatment of metastatic HNSCC refractory to standard platinum therapy, and in 2019 approval was extended to first line therapy.[14] While a majority of patients in this cohort, treated 2015–2019, did receive immunotherapy during treatment for DM. However, treatment with immunotherapy was not associated with improved survival. Reasons for receipt of immunotherapy may include disease refractory to cytotoxic chemotherapy signifying more aggressive disease or patient comorbidities that may preclude use of alternative therapies that could confound any associated survival benefit. HPV-negative patients are also more likely to receive immunotherapy for treatment of the first DM episode, potentially due to inability

to tolerate chemotherapy or more advanced disease states. These negative prognostic factors may confound any potential survival benefit seen in the subset of patients who might benefit from checkpoint inhibitor treatment.

In the multivariate analysis, HPV-positive tumor status was not independently associated with improved survival after distant progression. Instead, other factors associated with HPV-positive tumor status including lower comorbidity scores and longer time to DM progression were associated with improved survival. However, Charlson comorbidity scores were independently associated with decreased survival after distant progression, and HPV-negative were noted to have higher comorbidity scores. In addition, we found that distant metastasis limited to a single organ site was associated with improved survival after DM, while additional episodes of DM did not impact survival. LR recurrence was not independently associated with survival after in multi-covariate analysis. Other studies have shown a relationship between LR recurrence and survival after DM, regardless of HPV status.[5]

Late DM were also found to be associated with improved survival. In Kaplan–Meier survival analysis, patients with longer distant metastasis free interval (>1 year after primary treatment) had longer survival after distant progression. Our study did show a trend toward longer time to DM in HPV-positive patients, and previous studies have associated late recurrences with HPV positivity. The longer survivorship of HPV-positive patients may provide potential bias for the timeline of development of late metastases.[3,8,15]

M1 patients, with distant metastasis at the time of primary diagnosis, were not included in the main analysis. A separate Kaplan–Meier analysis comparing M1 at presentation versus M0 at presentation patients demonstrated that patients with M1 disease at presentation had significantly longer survival after distant progression, even when analysis was restricted to HPV-positive patients. We note that 50% of patients were treated aggressively with induction chemotherapy followed by definitive chemoradiation. Thus, M1 disease at presentation was treated aggressively with a subset receiving treatment with curative intent. More aggressive treatment of distant disease with curative intent has been established in prior studies to confer a survival advantage.[8,11] In an analysis of the National Cancer Database (NCDB), Kaplon et al. found that HPV-positive OPSCC patients presenting with M1 disease had significantly better survival than HPV-negative patients with M1 diasease.[16] In addition, patients presenting with M1 disease are likely to be chemo-naïve, increasing the potential efficacy of initial treatment.

Various studies have shown that survival in OPSCC patients can be relatively prolonged in patients even after disease progression. A 2014 study found a 2 year overall survival (OS) of 54.6% for HPV-positive patients versus 27.6% for HPV-negative patients after disease progression (local and/or DM) had previously been demonstrated.[2] Similarly, HPV-positive patients also have better outcomes in regards to DM. In a 2014 study of DM in p16-positive versus p16-negative patients, Sinha et al found p16 positivity, locoregional control, and *curative* DM treatment to be independently associated with improved post-DM survival.[8] In a 2015 study, OPSCC patients treated with surgical salvage of distant disease were associated with significantly improved 2-year survival when compared to patients receiving nonsurgical treatment (86.5% vs. 36.3%).[10] Understanding the potential for improved prognosis even after distant progression can guide decision-making and potentially consideration of curative therapy, especially in the era of immunotherapy.

We acknowledge some key limitations in our current study. This represents a retrospective review of a limited population of 87 patients (with 73 patients when M1 patients were excluded). However, given the relative infrequency of distant metastasis in OPSCC, particularly HPV-positive disease this still represents one of the largest published, as prior studies reported on a range of 37–79 patients.[2,5,7,8] Our institution is a quaternary care center where patients may not be fully representative of the general population. Additionally, some patients received primary treatment at outside institutions, and types treatment were not standardized across our patients with the treatment algorithm for treating DM was potentially affected by ongoing clinical trials. Furthermore, data regarding immunotherapy treatment were limited and biomarker data including PD-L1 expression were not available for this patient cohort. Lastly, due to the period of our study, the follow-up time of our study is limited, and we are also unable to account for patients who may have developed DM that might have been diagnosed and treated at another institution.

5 | CONCLUSIONS

Our data support previously published results showing better outcomes for patients with HPV-positive versus HPV-negative OPSCC disease with distant progression. Patients with metastasis at primary diagnosis (M1) had better survival after DM than patients that develop DM after initial treatment. This finding may be related to more aggressive curative therapy provided to these patients and has not been widely established in the

published literature and merits further investigation. In addition, multiple sites of DM and early DM were found to be a negative prognostic indicator for OPSCC patients with DM regardless of HPV status. Our findings also challenge the notion that HPV-positive DM is associated with explosive DM sites. It is noteworthy that the 2-year survival after DM reported is higher than historically published reports, particularly for HPV-positive patients, suggesting that current treatments inclusive of immunotherapy may hold greater promise for patients with OPSCC with DM. Several areas remain open for future investigation on potential for improving outcomes in these patients, such as further investigating the role of immunotherapy and curative treatment in this population.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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