Published in final edited form as:

Oral Oncol. 2014 January ; 50(1): 45–51. doi:10.1016/j.oraloncology.2013.10.007.

Distant Metastasis in p16-positive oropharyngeal squamous cell carcinoma: A critical analysis of patterns and outcomes

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Abstract

Objective—With good loco-regional control, disease failure in p16-positive oropharyngeal squamous cell carcinoma (OPSCC) mainly results from distant metastasis (DM). Our objective was to characterize the patterns and clinical outcomes of DM in p16-positive OPSCC and compare these to patients with p16-negative disease.

Methods—Primary OPSCC patients who developed DM after completing surgical or non-surgical treatment were identified and p16 status was evaluated. Patterns of DM and post-DM progression-free (PFS) and disease-specific survival (DSS) were assessed.

Results—Forty-one of the 66 (62%) patients with DM were p16-positive. DM patterns were not statistically different by p16 status. However, p16-positive patients developed DM later in their course and had longer survival. All p16-negative patients either had progression or died within 24 months of DM detection whereas the 2-year post-DM PFS in the p16-positive group was 20% (95% CI:8–32.5%,*p*=0.003). The 3-year post-DM disease-specific survival (DSS) estimate in the p16-positive patients was 16% (95%CI: 7–18%) while all p16-negative patients died within 34 months (*p*<0.001). p16-negativity, loco-regional disease, and no/palliative versus curative intent treatment were all associated with reduced post-DM DSS in multivariate analysis.

Conclusions—The DM pattern did not differ remarkably between p16-positive and negative OPSCC patients in our practice. In p16-positive OPSCC with pulmonary oligometastatic disease, curative intent treatment and optimized locoregional control for the index primary prolonged survival.

Keywords

Human papillomavirus; oropharynx carcinoma; distant metastasis; p16-positive; oligometastasis

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INTRODUCTION

Loco-regional control rates are excellent in the majority of p16-positive oropharyngeal squamous cell carcinoma (OPSCC) patients, and poor outcomes are mainly attributable to distant metastasis (DM). The DM rate varies from 5% – 12% in recent non-surgical series of OPSCC with known HPV/ p16 status,^{1–5} and from 2% – 6% in the surgical series.^{6–9} Emerging reports suggest that the DM patterns for p16-positive patients are atypical compared to those for p16-negative patients. As of now, the only evidence for such an observation comes from two case reports and two cohort studies which have focused on DM patterns in p16-positive OPSCC.^{5,10–12} The two cohort studies from University of Toronto observed the DM progression in p16-positive OPSCC to more often exhibit a “disseminating” pattern.^{5,10} The second report from this group expanded the study cohort from 36 to 79 patients with DM and reported longer survival in p16-positive patients.⁵ All patients in these studies were treated non-surgically.

The rapidly increasing numbers of p16-positive OPSCC at our institution with excellent loco-regional control and failures occurring mainly at distant sites provided the impetus to scrutinize DM patterns in our practice. Our patient population offered a unique opportunity to evaluate DM patterns in OPSCC patients treated both surgically and non-surgically.⁸

The primary aim of our study was, therefore, to characterize DM among p16-positive and negative OPSCC patients and to determine if there are any significant differences. Since the data on therapeutic outcomes after DM detection in this era of p16-positive OPSCC is still limited, the second objective of our study was to examine and compare the impact of treatment in both p16-positive and negative cohorts.

MATERIAL & METHODS

Study population

Our institutional review board-approved head and neck cancer surgery and radiotherapy registries were searched for primary OPSCC cases who received treatment at our institution from August 1997 to October 2011. The fundamental inclusion criteria were:

1. Previously untreated, biopsy-proven, primary OPSCC (Any T, any N, M0).
2. Completion of therapy (surgical or non-surgical) for primary OPSCC.
3. Development of DM after completion of therapy, verified by biopsy/resection or serial radiology scans.
4. Tissue available for p16 testing by immunohistochemistry (IHC).

Therapy for the oropharyngeal primary consisted of primary surgery ± adjuvant therapy or non-surgical modalities. Patients with a past history of head and neck SCC were excluded. Patients were also excluded if their disease status could not be ascertained at last follow up or at death. For patients treated prior to 2010, archival tissue specimens were procured for p16 IHC, according to standard protocols.¹³ Demographic, disease, treatment and outcome-related data were retrospectively collected from the medical charts. Information about survival status was obtained from the records and checked through social security death registries.

Primary Treatment

Non-surgical therapy included: (a) radiotherapy (RT) alone, (b) induction chemotherapy (CT) followed by concurrent chemoradiotherapy (CRT), and (c) concurrent CRT. For patients undergoing surgery for the primary tumor, transoral or non-transoral (pharyngotomy

and transmandibular) approaches were used. Neck dissection(s) were usually performed simultaneously with resection of the primary. Adjuvant therapy (RT or CRT) was administered for presence of high-risk pathological features as indicated.

Treatment for DM

Treatment administered after detection of DM was classified into: (1) None, (2) Curative, and (3) Palliative. Treatment was considered “*curative*,” if (a) surgery was performed with a curative intent resulting in margin-negative resection such as resection of limited pulmonary metastasis(es), or (b) radiation was delivered to the mediastinum or single DM focus in bone with curative intent. Surgical interventions performed only for diagnostic intent, unless they resulted in complete resection of DM, were considered “*palliative*” treatment, as were major debulking procedures, radiation in palliative dosage, and chemotherapy.

Study end points

The primary end points were pattern of DM and post-DM disease-specific survival (post-DM DSS). Pattern of DM was characterized as oligometastasis (limited to 1–2 anatomic sites or 3 metastatic foci in one anatomic site), disseminating (> 2 anatomic sites), or explosive²⁰ (4 foci of metastasis at one anatomic site), akin to the definitions by Huang et al.^{5,10} Post-DM DSS was calculated from the time of DM detection to death from disease (i.e. distant metastasis or disease progression at the distant and/or the locoregional site). Patients with any known disease, but who died of a co-morbid illness such as cardiovascular compromise, etc., were considered to still have died from disease. DSS was selected as a primary end-point because, although DM is often considered a terminal event, many patients experienced long term survival after it.

The secondary endpoint included post-DM progression-free survival (post-DM PFS). Post-DM PFS was defined as the time from detection of DM to death or disease progression at any (loco-regional and/or distant) site. The time interval for progression of DM was computed from the date of DM detection to progression on radiographic evidence of involvement of more sites or development of more foci at the same site. Patients who survived more than 24 months after detection of DM were defined as having “*long-term survival*” post-DM.

Statistical Analysis

Statistical analysis was conducted using SPSS software (IBM SPSS Statistics, Rel 20.0.0, Chicago: IBM Corporation) and STATA. Heterogeneity between any two groups was investigated using Chi-square or Fischer’s Exact Test for categorical data and independent *t* test for continuous data. Survival probability with 95% confidence intervals (CI) was estimated by the Kaplan-Meier method and compared with the log-rank test. For all analyses, statistical significance was indicated at a *p* value of < 0.05.

Factors prognostic for survival were investigated through univariate and multivariate Cox proportional hazard (PH) models. The 95% CI and *p* values were calculated for the hazard ratios (HR). The performance of multivariate models was compared by concordance index (C-statistic) and boot-strapping. The assumption of proportionality was tested and met for the Cox analysis. The C-statistic indicates a model’s ability to discriminate between patients with the event from those without it. Its value ranges from 0.5 to 1 where 1 reflects perfect discriminatory power.

RESULTS

Study Population

A total of 776 patients were identified from our registries who completed therapy for primary OPSCC. The disease status could not be ascertained for 13 patients, and 4 had DM at the time of primary OPSCC detection, thus leading to 17 exclusions. The remaining 759 patients consisted of 183 (24%) treated non-surgically and 576 (76%) treated surgically. A total of 84 (11%) patients developed DM, 41 (22%) in the non-surgical group and 43 (8%) in the surgical group. Tissue was available for p16 IHC for 66 of the 84 (79%) patients. Thus, 66 patients consisting of 61 (92%) men and 5 (8%) women, fulfilled all four eligibility criteria and comprised the final study cohort. p16 IHC was positive in 41 patients (62%) and negative in 25 (38%). The demographic, tumor stage, histology, treatment variables and outcomes as stratified by p16 status are presented in Table 1.

DM was detected during imaging as part of routine cancer surveillance in all except 2 patients in whom pleural effusion and vocal cord palsy (in one each) led to diagnostic imaging. The diagnosis of DM was histology-based (actual tissue or FNA) (Figure 1) in 48 of the 66 patients (73%). For the remaining 18 patients, the diagnosis was based on radiological evidence of DM through serial scans.

Primary treatment

Non-surgical (n=28)—Of the 15 p16-positive patients treated non-surgically, 2 (11%) received RT, 8 (36%) received induction CT + CRT while 5 (53%) received concurrent CRT. Amongst the 13 p16-negative patients, 1 patient received RT, 7 received induction CT + CRT and 5 received concurrent CRT. Twelve of the 28 (43%) patients had evidence of loco-regional disease within 1 to 6 months of treatment. Of these 12 patients, 4 were successfully salvaged with surgery, 4 received palliative chemotherapy, and the remaining 4 did not receive any treatment due to co-morbid illnesses or rapid development/ progression of DM.

Surgery ± adjuvant therapy (n=38)—Of the 26 p16-positive patients treated by surgery ± neck dissection(s), 18 underwent resection through transoral and 8 through an open approach. No adjuvant therapy was administered in 2 patients, 13 received RT and 11 had concurrent CRT. In the 12 p16-negative patients, 6 each underwent transoral and open resection. Four patients received no adjuvant, whereas 5 received RT and 3 CRT, respectively.

Pattern of disease recurrence

The pattern of recurrence (Table 1) differed between the p16-negative and p16-positive patients mainly for local recurrences (n=11/25,44% vs. n= 4/41,10%; p = 0.002). In the p16-positive group, the time to DM detection ranged from 1.1 to 106 months (median=12 months). In the p16-negative group, all cases were detected between 1.2 to 33 months (median= 8.4 months) from treatment completion.

Pattern and sites at first detection of DM

At the time of first detection of DM, although there were trends, the radiographical patterns did not differ significantly between the two groups (Table 1). Sites for the p16-positive DM were: lung (n=21,51%), bone (n=5,12%), isolated non-regional lymphadenopathy (n=3,7%), pericardium (n=2,5%), liver (n=1,2%), lung+liver (n=3,7%), lung+axillary nodes (n=2, 5%), lung+skin (n=1,2%), lung + chest wall (n=1,2%), lung+heart+pericardium (n=1,2%), bone +liver (n=1,2%).

Sites for the p16-negative patients were: lung (n=13,52%), bone (n=2,8%), liver (n=2,8%), scalp (n=1, 4%), lung+bone (n=2,8%), lung+liver (n=1,4%), liver+bone (n=1,4%), lung + liver + bone (n=1, 4%), lung+abdomen+bone+skin metastasis (n=2,8%). Interestingly, isolated non-regional lymphadenopathy (n=5), including axillary (n=2), mediastinal or pericardial nodes (n=3), was seen only in the p16-positive group.

Among the 6 p16-positive patients with bony metastases, the sites involved were: humerus, scapula, ribs + thoracic vertebrae, pelvis, femur, and lumbar vertebrae + sacrum + femur in one each. Among the 8 p16-negative patients with bony metastases, the sites involved were: frontal bone, humerus, ribs + thoracic vertebrae, pelvis+ lumbar vertebrae, humerus + ribs+ femur in one each, and pelvis in 3.

Pattern of DM progression

After detection of DM, 24 of the 66 patients died of disease (17 p16-negative, 7 p16-positive) and could not be followed for disease progression. This left us with 42 patients, 35 of whom developed DM progression (8 p16-negative, 27 p16-positive). For the other 7 patients (all p16-positive), 1 died of loco-regional disease with no progression at DM site, 3 were alive without disease, and 3 died of non OPSCC-related causes (see below under Survival).

Of 27 p16-positive patients with progression of their DM, the pattern was oligometastatic in 9, “explosive” in 11, “disseminating” in 2, and “explosive and disseminating” in 5. A total of 18 of 27 (67%) p16-positive patients had “explosive”, “disseminating”, or “explosive and disseminating” patterns compared to only 3 of 8 (37.5%) p16-negative patients. Thus, the rate of the “explosive and/or disseminating” pattern of DM in p16-positive patients was almost twice that of the p16- negative patients. This difference was not statistically significant ($p=0.22$), although the number of patients is small to make any definitive conclusions.

Loco-regional disease

Loco-regional disease was present at the time of DM detection or later in 52% (n=13/25) of the p16-negative patients compared to 25% (n=10/41) in the p16-positive patients ($p=0.022$). Higher frequency of loco-regional disease was seen in the p16-negative patients treated non-surgically (85%, n=11/13) vs. patients treated surgically for the index primary (17%, n=2/12, $p=0.001$) and also within the p16-positive patients (53%, n=8/15 in non-surgical vs. 15%, n=4/26 in surgical group, $p=0.015$).

In the surgically-treated patients, 3 of 26 (11.5%) p16-positive and 2 of 12 (16.7%) p16-negative patients had positive margins on the final pathology despite negative intra-operative frozen sections. All of these 5 patients received post-operative radiation. None of them had disease recurrence at the primary site, but one had regional recurrence.

Treatment and survival following DM diagnosis

The clinical courses following DM diagnosis in the p16-negative and positive cohorts are represented in Table 2.

Treatment—Of the 66 patients, 14 received no treatment due to death <2 months (n=6), unresectable locoregional recurrence (n=3), refusal (n=2), or multiple DM (n=1). Most of these 14 patients (78%, n=11) were p16-negative. Another 14 patients were treated with a “curative” intent while the remaining 38 received “palliative” therapy.

In the p16-positive patients, the chemotherapeutic drugs with which reduced volume or stable disease was recorded for a period of 6 months were gefitinib, temsirolimus, and panitumumab. None of the CT regimens stabilized disease progression for >2 months in the p16-negative group.

Survival—All p16-negative patients either had progression or died within 24 months of DM detection whereas the 2-year post-DM PFS in the p16-positive group was 20% (95% CI:8–32.5%, $p=0.003$). The 3-year post-DM DSS estimate in the p16-positive patients was 16% (95% CI:7–18%, $p<0.001$) while all p16-negative patients died within 34 months (Figure 2).

Overall in the p16-positive group, at last follow-up, 32 patients were dead of disease, 3 alive with no disease, 3 alive with disease, and 3 dead of non OPSCC-related causes. In the latter 3 patients, death occurred following a cardiovascular event in 2 and lower gastrointestinal bleeding in 1 patient at intervals of 27, 64, and 13 months, respectively, from the metastasectomy for lung oligometastases. At last follow-up before death (< 6 months), all 3 were disease-free, clinically and radiologically.

“Long-term survival”: There were 2(8%) “long-term” survivors in the p16-negative group versus 12(29%) in the p16-positive group ($p=0.061$). The treatment for the 2 p16-negative “long-term” survivors included debulking of lung metastasis+palliative CT in one and radiofrequency ablation (RFA) of a pelvic lesion+palliative CT in the other.

For the 12 p16-positive “long-term” survivors, “curative” treatment was administered in 8 and “palliative” in 4. Treatment included *curative* resection($n=3$), *curative* resection +palliative CT ($n=3$), *palliative* resection+CRT ($n=2$), *palliative* resection+ CRT ($n=2$), *palliative* RT ($n=1$), and *palliative* CT ($n=1$). All these patients had oligometastatic disease in lung except one with lung and dermal metastasis over the lower neck and upper chest wall.

Curative therapy with or without palliative CT in p16-positive group: The 3-year post-DM DSS in p16-positive patients with “curative” intent therapy was 40% versus 8% in patients with “palliative” therapy (Figure 3). Amongst the “curative” intent-treated p16-positive patients, post-DM DSS estimates were not different ($p=0.148$) between patients receiving palliative CT (50%, 95% CI:16–84) and those without it (80%, 95% CI:45–100). Three of 6 (50%) patients in the “curative therapy with palliative CT” group were long-term survivors compared to 3 of 5 (60%) patients in the “curative therapy without palliative CT” group. Three of 6 patients in the “curative therapy with palliative CT” group experienced complications of severe thrombocytopenia, pulmonary embolism, and neutropenic fever with bacteremia in one each. The latter two required hospitalization.

Cox analysis for post-DM survival: In univariate analysis for post-DM DSS, p16-negative vs. positive status (HR=2.7, 95% CI:1.6–4.7, $p<0.001$), locoregional disease vs. none (HR=2.1, 95% CI:1.2–3.7, $p=0.009$), and no/palliative treatment vs. curative intent DM treatment (HR=4.0, 95% CI:1.87–8.59, $p<0.001$) were associated with reduced survival.

Multivariate analysis identified two models that were predictive of post-DM DSS. The first model with the variables of p16 negative vs. positive status (HR=2.5, 95% CI:1.5 – 4.4, $p=0.001$) and no/palliative vs. curative intent (HR=3.8, 95% CI:1.7–8.2, $p=0.001$) had a C-statistic of 0.71(95% CI:0.66 – 0.77). The second model with the variables of p16 negative vs. positive status (HR=2.5, 95% CI:1.4 – 4.3, $p=0.001$) and locoregional disease vs. none (HR=1.8, 95% CI:1.01– 3.2, $p=0.045$) had a C-statistic of 0.65(95% CI:0.59–0.72).

DISCUSSION

In our study, we observed that p16-positive OPSCC patients develop DM after more prolonged periods following completion of primary treatment compared to p16-negative patients. However, we found that the pattern of DM in the p16-positive patients, although slightly trending towards wider disease spread, as reported in previous studies,^{17,20,21} was not significantly different than the p16-negative patients ($p=0.615$). We also noted that DM in p16-positive OPSCC, particularly pulmonary oligometastatic disease, was relatively indolent, treatment-responsive and was associated with longer survival. Reduced survival was observed with recurrent/ persistent loco-regional disease, the frequency of which was significantly higher in the p16-negative patients, particularly those treated non-surgically.

Time to DM

In our p16-positive cohort, 17% developed DM more than 2 years after treatment, and the maximum interval to DM detection was 9 years. This is consistent with the recent literature. Huang et al⁵ also reported a prolonged time interval from treatment to DM detection in p16-positive OPSCC. These observations emphasize the importance of longer term surveillance for DM in these patients.

Pattern of DM

With the exception of the pericardium, sites for DM were similar in both the p16-positive and negative groups. However, non-regional lymphadenopathy (axillary, pericardial, mediastinal, intra-abdominal) was more commonly seen with p16-positive OPSCC. Even during progression, bulky nodal lymphadenopathy was observed. This may be similar to how the disease behaves in the head and neck. Another pattern of DM recently noted as *unusual* in 3 of a series of 4 p16-positive patients is the presence of bone-only metastases.¹¹ In our study, bone-only metastases were found in 12% of the p16-positive patients compared to 8% in the p16-negative patients. Moreover, the sites of bony metastasis in our p16-positive patients were not different from those in p16-negative patients. Most of the bony metastasis sites reported by Müller et al. (with the exception of sternum and clavicle)¹¹ were those seen in both our p16-positive and p16-negative patient cohorts.

Similar to Huang et al,⁵ DM progression varied slightly within the p16-positive patients. Approximately 50% of patients progressed to involve more than one site. However, no unique factors underlying such variation were identified. In our study, even though the “disseminating” phenotype was almost twice as common in the p16-positive group, the difference was not statistically significant. This could be due to the fact that most of the p16-negative patients had an aggressive course of disease and died before their pattern of DM progression could be evaluated. Other authors have invoked the concept that it is due to intrinsically different tumor biology.^{5,10,14}

Post-DM survival and prognostic factors

The independent variables associated with better survival were: (1) p16-positive disease, (2) loco-regional control, (3) DM treatment with *curative* intent. Post-DM PFS and DSS were significantly greater in the p16-positive patients. Moreover, a higher frequency of “long-term” survivors was seen among them ($p=0.002$). Huang et al also recorded longer overall survival for p16-positive patients, although DSS was not reported in their study.⁵ The prognosis following DM detection in chemical carcinogen-associated SCC is generally dismal and mortality is reported to occur in at least 90% within the first 12 months,¹⁵ so the finding that some p16-positive OPSCC patients live for long periods after the development of DM is significant.

Locoregional control is a well-established predictor for the development of DM in SCC of the oropharynx and other head and neck sites^{16–18} but we also found it to be a significant factor for survival with already established DM. The loco-regional control rate was significantly better in the p16-positive group with DM. Compared to the p16-negative patients, the p16-positive cohort had a preponderance of cT1-T2 primaries (28% vs. 44%) and of surgical treatment (48% vs. 63%), although these differences were not statistically significant. Neither of the latter two variables impacted the post-DM survival independently. However, persistence of loco-regional disease was seen in 43% of our non-surgically treated patients. This could have contributed to the development of DM and to poorer post-DM survival. These findings support the practice of complete removal of the index primary and the neck nodes to achieve excellent locoregional control, as long as this can be achieved with minimal morbidity. Salvage surgery for residual locoregional disease following completion of primary non-surgical treatment may also be important for prolonging survival in p16-positive OPSCC patients, particularly those with oligometastatic disease. Again, however, the morbidity of such procedures needs to be carefully considered.

Surgical resection for oligometastatic disease (n=18, curative or palliative), particularly in lung, resulted in long term survival (n=10) and even “cure” (n=6) in a substantial number of patients. Imaging modalities such as PET-CT allow detection of oligometastatic disease in an efficient manner. Hence when detected and confirmed by biopsy, such disease should probably be treated with a “curative” intent. Numerous reports, both in the settings of head and neck carcinoma^{19–21} and other sites (e.g. non-small cell lung carcinoma) have observed prolonged survival with surgical resection of the oligometastases.²² Palliative chemotherapy after margin-negative surgical resection of oligometastatic disease should be used judiciously in view of the substantial risk of treatment-related morbidity. However, it may be the only therapeutic option available if the disease progresses even after curative intent treatment, particularly in patients with good performance status.

The use of targeted molecular therapy was associated with prolonged post-DM PFS in 3 of our p16-positive patients. EGFR (epidermal growth factor receptor) and mTOR (mammalian target of rapamycin) were the molecular targets. A detailed discussion of the underlying mechanisms is beyond the purview of our article, but future studies may evaluate them for targeting distant metastatic disease in p16-positive OPSCC.

Limitations

Lack of p16 IHC testing on all DM patients limited the sample size. The study spanned a long time period, during which treatment concepts for the primary tumors and the DMs evolved, as did the knowledge about p16 as a prognostic marker, although it was not used as a therapy-determining factor. Selection biases may have also occurred in the treatment pathways for the index primary tumors in our study, but it was not our objective to specifically compare the DM pattern between treatment groups. We assessed the presence or absence of DM in all primary OPSCC patients treated at our institution with surgical or non-surgical modalities to avoid bias which would have resulted from examining patients treated with only one treatment modality. Moreover, by determining the DM pattern against p16-negative OPSCC as controls, we sought to minimize selection bias which would have resulted from examining only the p16-positive patients with DM.

Conclusions

We have detected a level of survivorship in p16-positive OPSCC patients with DM which approaches 16% at 3 years. If suitable for curative intent treatment, the results were even better, with 40% survivorship at 3 years. By contrast, the majority of p16-negative patients died early in the course after DM detection. In comparison with p16-negative patients who

survived long enough to have documented DM progression, the pattern of DM in p16-positive patients did not differ significantly. Our study is the first to give detailed documentation of the prognostic factors including the impact of therapeutic options for p16-positive OPSCC with DM. In patients with pulmonary oligometastases, it is important to adopt an expeditious treatment approach with curative intent including surgical interventions to prolong survival. Loco-regional disease is also an important factor for post-DM survival. Hence, in selected patients with pulmonary oligometastases, treatment should be optimized to ensure good loco-regional control to prolong survival. Furthermore, in certain p16-positive patients with progressive disease failing traditional chemotherapeutic agents, there may be a potential for newer molecular targeted therapies to suppress disease progression.

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Figure 1. Histologic features of nonkeratinizing squamous cell carcinoma with distant metastasis to the lung. A – Low power (4× magnification), and B) High power (inset shows p16 staining) (both 20× magnification).

Figure 2.
Kaplan Meier estimates for (A) Post-Distant Metastasis Disease-specific survival ($p < 0.001$), (B) Post-Distant Metastasis Progression-free survival by p16 status ($p = 0.003$)

Figure 3.
Kaplan Meier estimates for Post-Distant Metastasis Disease-specific survival in p16-positive patients by types of therapy ($p < 0.001$)

Table 1Patient and tumor 1 characteristics by p16 status¹

	Category	p16-negative n=25 (38%)	p16-positive n=41 (62%)	p-value ²
Age	Mean (years)	56	57	0.649
	Median (Min– Max)	55.5 (44–74)	56.4 (35–77)	
Gender	Male	22 (88)	39 (95)	0.289
	Female	3 (12)	2 (5)	
Race	African-American	10 (40)	1 (2)	<0.001
	Caucasian	15 (60)	40 (98)	
Tobacco	Never	2 (8)	12 (29)	0.001
	Former	7 (28)	21 (51)	
	Current	16 (64)	8 (20)	
Comorbidity (ACE 27)	None-Mild (0–1)	19 (76)	33 (80)	0.665
	Moderate-Severe (2–3)	6 (24)	8 (20)	
Site	Tongue base	6 (24)	18 (44)	0.103
	Tonsil	19 (76)	23 (56)	
cT classification	T1–T2	7 (28)	18 (44)	0.196
	T3–T4	18 (72)	23 (56)	
cN classification	N0	3 (12)	1 (2)	0.216
	N1–N2a	6 (24)	8 (20)	
	N2b–N3	16 (64)	32 (78)	
Primary Treatment	Surgery	12 (48)	26 (63)	0.219
	Non-Surgery	13 (52)	15 (37)	
Time to DM from therapy(months)	Mean	10.8	16	0.196
	Median (Min–Max)	8.4 (1.2 – 33)	12 (1.1 – 106)	
DM pattern at detection	Oligometastasis	10 (40)	19 (46)	0.615
	Disseminating/explosive	15 (60)	22 (54)	
Pattern of first recurrence	Distant only	13 (52)	29 (71)	-
	Distant + Local	4 (16)	1 (2)	
	Distant + Regional	1 (4)	4 (10)	
	Distant + Loco-regional	3 (12)	2 (5)	
	Local	2 (8)	0	
	Regional	0	4 (10)	
Loco-regional disease at/after DM detection	Loco-regional	2 (8)	1 (2)	
	No	12 (48)	31 (76)	0.032
	Yes	13 (52)	10 (25)	

DM=Distant metastasis;

¹ p16 defined as positive when >50% of tumor cells have nuclear and cytoplasmic staining² values in bold are statistically significant (<0.05)

Table 2

Clinical course after detection of distant metastasis (DM)

	Category	p16-negative n=25 (38%)	p16-positive ⁴ n=41 (62%)	p-value ³
Pattern of DM progression	No progression	17 (68) ¹	14 (34) ²	0.221
	Oligometastasis	5 (20)	9 (22)	
	Disseminating/explosive	3 (25)	18 (44)	
Therapy for DM	None	11 (44)	3 (7)	0.002
	Curative	3 (12)	11 (27)	
	Palliative	11 (44)	27 (66)	
Long-term survival	No	23 (92)	29 (71)	0.03
	Yes	2 (8)	12 (29)	
Post-DM Progression-free survival (months)	Mean	5	14	0.007
	Median (Min–Max)	2.7 (0.3 – 19)	7 (0.2 – 88)	
Post-DM disease-specific survival (months)	Mean	7.7	19	0.002
	Median (Min–Max)	3.8 (0.3 – 34)	13.8 (0.6 – 88)	

¹ Died before documentation of DM progression;² 8 died of disease before documentation of DM progression, 3 are alive without disease, 3 died of other causes;³ values in bold are statistically significant (<0.05);⁴ p16 defined as positive when >50% of tumor cells have nuclear and cytoplasmic staining