



Heterogeneity in the clinical presentation, diagnosis, and treatment initiation of p16-positive oropharyngeal cancer

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ABSTRACT

Background: Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) has a patient demographic, presentation, and clinical treatment response distinct from HPV-unassociated OPSCC. The heterogeneity in presentation and diagnosis within a patient population with HPV-positive OPSCC and its impact on times to presentation, diagnosis, and treatment have yet to be characterized.

Participants: Patients with biopsy-proven p16-positive OPSCC seen and/or treated at our institution between 2008 and 2018. Of 136 patients with OPSCC seen and/or treated at our institution, 101 met criteria for inclusion.

Methods: Patients were grouped by several parameters including presenting symptom category (asymptomatic neck mass, neck mass with primary-site symptoms, or primary-site symptoms without a neck mass), p16 status on fine-needle aspiration (FNA), and date of presentation. Median time intervals between presentation to imaging, biopsy, and treatment were compared within each parameter using the Kruskal-Wallis test with a significance level of 0.05.

Results: Sixty-five of the 101 study patients presented with a neck mass. Patients without a neck mass had a longer interval from presentation to imaging than patients with a neck mass (median 4 vs 0 days, $p = 0.025$). Initial FNA obtained on 61 patients was positive for p16 in 19 patients. Unknown or negative p16 status on FNA was associated with shorter intervals from initial imaging to treatment initiation (39 vs 46.5 days, $p = 0.045$). Patients presenting in the final three years had a longer interval from presentation to treatment initiation (55 vs 41 days, $p = 0.024$).

Conclusion: A neck mass is absent from the clinical picture of a substantial proportion of HPV-associated OPSCC patients. Primary-site symptom category and regional metastasis were not associated with differences in times to diagnosis or treatment initiation at this major referral center. The increased awareness and complexity of treatment decisions related to OPSCC may contribute to the delays in treatment initiation observed in patients with p16-positive FNAs and those who presented in more recent years.

1. Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) associated with human papillomavirus (HPV) is increasing despite the downward trend in overall incidence of head and neck cancers over the past 20 years [1]. At the current rate, it is projected to surpass that of cervical cancer, the malignancy primarily associated with HPV, by

2020 [1].

HPV-associated OPSCC is viewed as an entity unique from its traditional HPV-unassociated counterpart on the basis of its distinct patient demographic, more favorable prognosis, and more sensitive clinical response to treatment [2]. The typical HPV-associated OPSCC patient is younger, of higher socioeconomic status, more likely to be male, and less likely to have a history of alcohol and tobacco use

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compared to the HPV-unassociated OPSCC patient [3–6]. HPV-positive patients are more likely to report an asymptomatic neck mass as their presenting symptom, whereas HPV-negative patients are more likely to initially report throat pain, dysphagia, and odynophagia [3,5]. This discrepancy exists likely because HPV-positive tumors characteristically present with smaller primary lesions and cervical lymph node metastases that result in a neck mass without primary-site symptoms [3,6,7].

Other distinguishing features of HPV-associated OPSCC are the pathway to its diagnosis and its improved treatment response and prognosis. Since HPV-positive patients are more likely to present with an asymptomatic neck mass representing metastatic cervical lymphadenopathy, they will often undergo a fine-needle aspiration (FNA) of the mass [8,9]. FNA of cervical lymph nodes with cytological analysis is an efficient, cost effective procedure with low risks of complications that can reliably detect the presence of metastatic HPV-related head and neck cancer [7,9,10]. In the event that FNAs and core-needle biopsies are nondiagnostic, open cervical lymph node biopsy may be performed without complicating future treatment decisions or affecting survival [9,11]. As a consequence of the improved clinical treatment response and prognosis of HPV-associated OPSCC, a new staging system was implemented for p16-positive OPSCCs [12].

Due its unique and often cryptic presentation, swift diagnosis of HPV-associated OPSCC can be challenging despite the existence of workup algorithms and guidelines [9,13]. In their study comparing the establishment of diagnosis of HPV-positive OPSCCs to that of HPV-negative cancers, Truong Lam et al. demonstrated that a significantly higher proportion of HPV-positive patients required repeated biopsy procedures compared to HPV-negative patients [14]. Furthermore, patients with HPV-associated cancers were more likely to have their disease misattributed to another cause and thus have an unanticipatedly protracted interval from initial presentation to confirmation of diagnosis than patients with HPV-negative cancers [14]. Delays in treatment initiation, specifically from diagnosis to surgery and surgery to radiation therapy, are associated with significantly worse overall survival in patients with OPSCC, and delays in radiotherapy are associated with decreased survival in patients with HPV-positive tumors [15].

There is a need for expeditious diagnosis and treatment initiation of HPV-associated OPSCC given its rising incidence, its tendency to metastasize to cervical lymph nodes early without giving rise to overt symptoms or mucosal changes, and the likelihood of requiring multiple biopsies for diagnosis. The aims of the present study are to (1) further characterize the presentation and diagnosis of HPV-associated OPSCC, and (2) determine if the variability in presentation and diagnosis of OPSCC within an HPV-positive patient population impacts times to presentation, diagnosis, and treatment initiation.

2. Materials and methods

After obtaining Institutional Review Board approval, we conducted a retrospective chart review of patients diagnosed with oropharyngeal cancer with p16 positivity who received any component of care at our institution between 2008 and 2018. Inclusion criteria included patients diagnosed with OPSCC with documented HPV-positive tumor status via p16 immunohistochemistry, HPV DNA in-situ hybridization, or immunoperoxidase stain for high-risk HPV when available. p16, a tumor suppressor protein whose cellular expression increases following infection and inactivation of Rb by HPV, was used as a surrogate marker for HPV status due to its high sensitivity, prognostic value, and relative ease of use [6,16].

Clinical data were collected from electronic medical records. Data included age at presentation, gender, race, date of symptom onset, presenting symptoms, date of presentation, date of initial imaging, date of initial biopsy, type of initial biopsy, date of resection (if applicable), and dates of chemoradiation therapy initiation and completion (if applicable). Date of treatment initiation was defined as either the date of

Date of symptom onset to date of initial presentation
Date of initial presentation to date of initial imaging
Date of initial presentation to date of initial FNA (if obtained)
Date of initial presentation to date of initial non-FNA biopsy (if obtained)
Date of initial presentation to date of treatment initiation
Date of initial imaging to date of treatment initiation
Date of initial FNA (if obtained) to date of treatment initiation
Date of initial non-FNA biopsy (if obtained) to date of treatment initiation
Date of treatment initiation to date of treatment completion

Fig. 1. Time intervals used for comparison.

resection (if applicable) or chemoradiation therapy initiation if primary resection was not performed. Clinical T and N stages and smoking history were also collected. Date of symptom onset was approximated by the clinical note if an exact date was not specified in the initial presentation or consultation note. Presenting symptoms were categorized as follows: (1) neck mass without any other symptoms; (2) primary-site symptoms without neck mass (including sore throat, dysphagia, odynophagia, ear pain, and bleeding); (3) neck mass with primary-site symptoms; and (4) no symptoms. Date of initial presentation was noted as the earliest date that the patient presented to any provider (such as a primary care physician, an otolaryngologist at an outside institution, or an otolaryngologist at our institution) for evaluation of head and neck symptoms pertaining to a future diagnosis of oropharyngeal OPSCC. Smoking status was dichotomized as ≤ 10 pack-years and > 10 pack-years, as this cutoff is used for risk stratification of OPSCC as defined by Ang et al. [2]

The time intervals calculated are listed in Fig. 1. Patients were sorted based on the following parameters: age (< 60 or ≥ 60), presenting symptom category, FNA status, FNA p16 status, initial biopsy type, number of biopsies, resection status, date of presentation (within the first seven years of the study versus within the final three years of the study), smoking history, T stage, and N stage. p16 positivity was defined as $> 70\%$ staining by immunohistochemistry. Median time intervals were calculated and compared within each category using the Kruskal-Wallis test with a significance level of 0.05. All statistical analyses were performed using SAS version 9.4.

3. Results

Between 2008 and 2018, 136 patients with oropharyngeal cancers were seen and/or treated at our institution. p16 was negative for 10 of these patients, and of the remaining 126 patients, 25 were excluded from the study because their HPV status was unknown or their chart contained insufficient information about their presentation, diagnosis, or treatment. Of the 101 patients included in the study, 84 (83.2%) were Caucasian, 92 (91.1%) were male, and average age of diagnosis was 59.4 years. Baseline characteristics regarding diagnosis and treatment of the HPV-positive OPSCC patients are listed in Table I. Comparisons of median time intervals for categories of selected parameters by which the study patients were sorted are depicted in Fig. II.

3.1. Presenting symptom type

Forty patients presented with an asymptomatic neck mass, 34 patients presented with primary-site symptoms without a neck mass, 25 patients presented with both sets of symptoms, and 2 patients presented with no symptoms. Of the 40 patients presenting with a neck mass, an FNA was obtained on 36. Among the 34 patients who presented with primary-site symptoms only, 7 had an FNA. Of the 25 patients who presented with both sets of symptoms, an FNA was obtained on 17.

Table I
Baseline characteristics regarding diagnosis and treatment.

Baseline characteristics	Number of patients
Presenting symptom category	
Asymptomatic neck mass	40
Primary-site symptoms only	34
Neck mass + primary site symptoms	25
No symptoms	2
Smoking status	
0–10 pack-years	60
> 10 pack-years	39
FNA obtained	61
FNA positive for p16	19
Initial non-FNA biopsy type	
Tissue sample	27
Tonsillectomy	8
Direct laryngoscopy with biopsy	35
Open biopsy of cervical lymph node	8
Number of biopsies, not including FNA	
0	23
1	67
2	10
3	1
T stage	
1	17
2	44
3	17
4	9
N stage	
0	10
1	23
2	47
3	5
Underwent resection	49

Compared to patients who presented with an asymptomatic neck mass or a neck mass with primary-site symptoms, patients who presented with primary-site symptoms only had a longer interval from presentation to initial imaging (median 4 vs 0 days, $p = 0.025$). The presence of a neck mass with or without symptoms did not affect intervals to diagnosis or treatment initiation, as presenting symptom category was not associated with any significant differences in these intervals.

3.2. FNA status and FNA p16 status

An FNA was obtained for 61 of the 101 total patients. When comparing median time intervals between patients for whom an FNA was obtained and those for whom an FNA was not obtained, no significant differences in times to presentation, diagnosis, or treatment initiation were noted. Of the 61 patients for whom an FNA was obtained, a p16 immunohistochemical stain came back positive for 19 patients. Of the remaining 42 patients, p16 status on FNA was unknown or not obtained for 40 patients and negative for 2 patients. Two significant differences in time intervals were noted when comparing patients with a positive p16 status on FNA to those with an unknown or negative p16 status on FNA (Table II). Compared to patients with positive p16 status on FNA, those with unknown or negative p16 status on FNA had a shorter median interval from initial imaging to treatment initiation (39 vs 46.5 days, $p = 0.045$) and initial non-FNA biopsy to treatment initiation (32 vs 40.5 days, $p = 0.049$).

3.3. Clinical T and N stage

Median time intervals for patients with clinical T1 and T2 tumors were compared to those for patients clinical T3 and T4 tumors. Patients with T1 and T2 tumors had a significantly shorter interval from symptom onset to presentation than those with T3 and T4 tumors (35 vs 54 days, $p = 0.038$). No other differences in median time intervals were noted. Median time intervals for patients with clinical N0 and N1 disease were compared to those for patients with clinical N2 and N3 disease. Patients with N0 and N1 disease also had a significantly shorter interval from symptom onset to presentation than those with N2 and N3 disease (25 days vs 44 days, $p = 0.041$). No other differences in median time intervals were noted.

3.4. Resection status and smoking status

Forty-nine of the 101 total patients underwent primary resection for their tumors. Compared to patients treated nonsurgically, those who underwent definitive resection had shorter intervals from initial FNA to treatment initiation (24 vs 41 days, $p = 0.042$) and initial non-FNA biopsy to treatment initiation (24.5 vs 40 days, $p = 0.011$) but a longer interval from treatment initiation to treatment completion (87 vs 50 days, $p < 0.0001$). No significant differences in time intervals were noted when comparing patients with a smoking history ≤ 10 pack-years

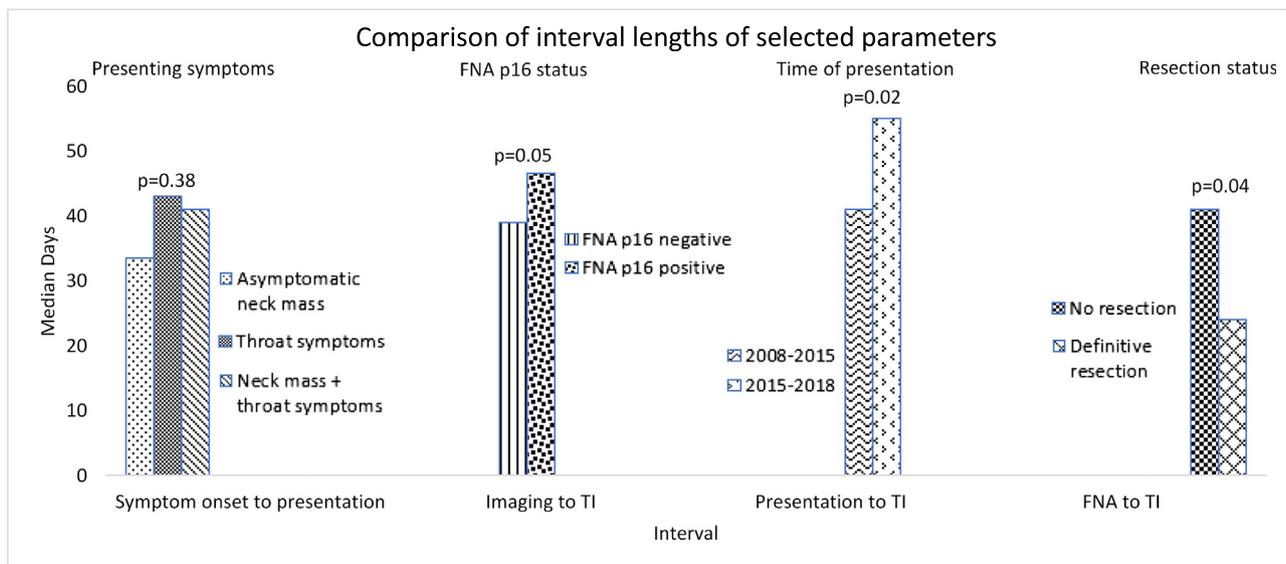


Fig. II. Time interval lengths for categories of various parameters including presenting symptom category, FNA p16 status, time of presentation, and resection status. TI = treatment initiation.

Table II

Comparison of intervals between patients whose FNAs were positive for p16 and those whose FNAs were unknown or negative for p16.

Interval	Median time interval, FNA p16 negative/unknown (days)	Median time interval, FNA p16 positive (days)	p-value
Symptom onset to presentation	40.5	31	0.804
Presentation to imaging	0	1	0.437
Presentation to FNA	9	19	0.034
Presentation to initial non-FNA biopsy	20	37	0.058
Presentation to treatment initiation	48	55.5	0.083
Imaging to treatment initiation	39	46.5	0.045
FNA to treatment initiation	34	40.5	0.089
Initial biopsy to treatment initiation	32	40.5	0.049
Treatment initiation to treatment completion	71	54.5	0.159

to those with a > 10 pack-year smoking history.

3.5. Number of biopsies, not including FNA

The number of non-FNA biopsies obtained for each patient was recorded. Twenty-three patients had no non-FNA biopsies, 67 patients had 1 such biopsy, and 11 patients had ≥ 2 such biopsies. Compared to patients who underwent 0 or 1 non-FNA biopsies, patients for whom ≥ 2 such biopsies were obtained had a significantly longer interval from presentation to treatment initiation (118 vs 43.5 vs 48.5 days, *p* = 0.012). No other differences in intervals to diagnosis were observed.

Age

The median age at presentation was 60. Forty-eight patients were diagnosed at < 60 years of age, and 53 patients were ≥ 60 years of age at diagnosis. When comparing patients < 60 years of age to those ≥ 60 years of age, no significant differences in median times to presentation, diagnosis, or treatment initiation were noted.

3.6. Date of presentation

Our institution experienced higher numbers of HPV-positive OPSCC patients in recent years, with 43 patients presenting in the first seven years and 58 patents presenting in the final three years of the study inclusion dates. Compared to patients who presented in the first seven years, those who presented in the final three years had a longer interval from presentation to initial FNA (14 vs 4 days, *p* = 0.003), presentation to treatment initiation (55 vs 41 days, *p* = 0.024), initial imaging to treatment initiation (44 vs 38 days, *p* = 0.038), initial FNA to treatment initiation (39 vs 30 days, *p* = 0.038), and initial non-FNA biopsy to treatment initiation (35.5 vs 28.5 days, *p* = 0.039) (Table III).

4. Discussion

HPV-associated OPSCC has been the focus of attention in recent years due to its rising incidence and differences in patient demographics, presentation, prognosis, and treatment compared to its

traditional HPV-unassociated counterpart. To date, no study has examined the potential heterogeneity inherent within the p16-positive patient population itself. Understanding the variability in presentation and diagnosis of HPV-positive cancers has the potential to expedite treatment initiation in this patient population. Based on the findings that HPV-associated OPSCC patients are more likely than HPV-negative patients to present with an asymptomatic neck mass and have a protracted interval from presentation to diagnosis, we postulated that HPV-positive patients with an asymptomatic neck mass would have longer intervals from symptom onset to presentation, presentation to diagnosis, and time to treatment initiation than patients without a neck mass.

At our institution, considerable variability exists in presenting symptom type even in patients with p16-positive disease. Of the 101 p16-positive patients in our study, about one-third presented without a neck mass, while close to two-thirds presented with a neck mass with or without primary-site symptoms. The proportion of p16-positive patients who presented without a neck mass at our institution mirrors the proportion of HPV-positive patients without a neck mass in the study by Truong Lam et al. [14] Although a higher proportion of p16-positive patients present with a neck mass than without a neck mass, our data serves as a reminder that the presence of primary-site symptoms in the absence of a neck mass does not rule out the possibility of HPV-associated disease.

Interestingly, our data revealed that presenting symptom category only affected one interval calculated in our study: the absence of a neck mass delayed the interval to initial imaging. A possible explanation for this finding may be that primary-site symptoms in the absence of a neck mass were initially attributed to a non-neoplastic process. However, the type of presenting symptom within a p16-positive patient population treated at our institution had no impact on time intervals to presentation, biopsy, or treatment initiation. It is possible that despite the differences in presentation, the pathogenesis behind the development of these HPV-positive tumors is the driving factor behind the similarities of these time intervals.

Our study also demonstrated that obtaining an FNA interestingly did not impact diagnosis or treatment times. While FNA is a convenient

Table III

Comparison of intervals between patients who presented in the first seven years of the study and patients who presented in the final three years of the study inclusion dates.

Interval	Median time interval, patients presenting in first 7 years (days)	Median time interval, patients presenting in final 3 years (days)	p-value
Symptom onset to presentation	50	35	0.230
Presentation to imaging	0	1.5	0.108
Presentation to FNA	4	14	0.003
Presentation to initial non-FNA biopsy	22	22	0.819
Presentation to treatment initiation	41	55	0.024
Imaging to treatment initiation	38	44	0.038
FNA to treatment initiation	30	39	0.038
Initial biopsy to treatment initiation	28.5	35.5	0.039
Treatment initiation to treatment completion	63	82	0.112

method to detect regionally metastatic disease, our data indicates that it does not necessarily expedite diagnosis or treatment in this p16-positive patient population. However, p16 status on FNA did impact interval to treatment: specifically, patients whose FNAs were p16-positive had longer intervals from initial imaging and non-FNA biopsy to treatment initiation than patients whose FNAs were p16-negative or unknown. Patients with p16 positivity on FNA may have sought additional opinions before initiating treatment, contributing to the delayed interval to treatment initiation.

Regarding clinical T and N stage, the only significant difference noted was that patients with earlier T and N stages had a shorter interval from symptom onset to presentation than patients with later T and N stages, likely because later stage disease took longer to develop. Although HPV-associated OPSCC patients typically present with low T stage and high N stage tumors, at our institution, the early T stage patients had lower N stage disease as well, whereas the later T stage patients had higher N stage disease.

As expected, patients who had ≥ 2 non-FNA biopsies had a longer interval from presentation to treatment initiation than patients with fewer than two such biopsies. Furthermore, patients who underwent primary resection instead of chemoradiation for their disease had shorter intervals from initial biopsies to treatment initiation but a longer total treatment package time. These findings can be explained by the time required for preparation of definitive chemoradiation and the six-week interval between surgery and adjuvant treatment. Although age at presentation was not associated with any difference in times to presentation, diagnosis, or treatment initiation, age is of paramount importance given its prognostic significance and the increasing proportion of p16-positive disease among older adults [17].

In recent years, our institution experienced a higher volume of patients with HPV-associated OPSCC. Over the last three years specifically, our multidisciplinary tumor board began adopting a patient-tailored approach including consideration of both surgical and nonsurgical options for HPV-associated OPSCC patients. The changes in staging guidelines and the consideration of both surgical and nonsurgical approaches for p16-positive patients may contribute to the delay in treatment initiation observed in the 58 patients who presented in the final three years of the study dates. Additionally, it is possible that in the more recent years, patients obtained opinions from a greater number of providers prior to undergoing diagnostic procedures or initiating treatment. Finally, smoking history as classified by ≤ 10 pack-years and > 10 pack-years failed to elucidate any differences in intervals to presentation, diagnosis, or treatment.

Our findings demonstrate considerable variability in presentation and diagnosis of HPV-associated OPSCC. Perhaps the most surprising finding was that within a patient population later determined to be p16-positive, presenting symptom category did not impact time to presentation, diagnosis, or treatment, but the presence of a neck mass was associated with a more rapid interval to initial imaging. Interestingly, an unknown or negative p16 status on FNA hastened treatment initiation even though these patients were later found to be p16-positive through other means. Our study adds to the growing body of literature characterizing HPV-associated OPSCC, confirming that despite the heterogeneity in presentation, patients with p16-positivity seen and treated at our institution have similar intervals to presentation, diagnosis, and treatment initiation when categorized by age, presenting symptom type, initial biopsy type, and smoking status. We postulate that these intervals would be different from those of an p16-negative patient population.

This study has several limitations. The retrospective nature of this study increases the risk of bias. Patients whose HPV status was unknown or charts contained insufficient data were excluded from the study, further increasing the risk of bias. Additionally, the exploratory nature of this single-institution study and institution-specific factors such as diagnostic and treatment algorithms may limit the

generalizability of these results. *P*-values should be considered descriptive rather than inferential and have not been corrected for multiple tests. Finally, the study lacked a large enough sample in order to properly conduct a multivariable analysis.

5. Conclusion

Although patients with HPV-associated OPSCC are more likely than HPV-unassociated OPSCC patients to have a protracted interval from presentation to diagnosis, the variability of presentation and diagnosis within an HPV-positive patient population, and its impact on diagnosis and treatment times, has not yet been characterized in detail. Patients with HPV-positive OPSCC had a heterogeneous presentation at our institution, but the presenting symptom category did not affect the time interval to presentation, diagnosis, or treatment. Patients whose FNAs were positive for p16 and those who presented in more recent years had delayed intervals to treatment initiation. These findings suggest that the increased awareness and complexity of treatment decisions related to OPSCC may affect times to diagnosis and treatment initiation in patients with HPV-positive disease.

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