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Is HPV-Associated Oropharyngeal Cancer Becoming More Common in Older Patients?

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Objective: To evaluate changing age demographics over a 15-year period for patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

Study Design: Retrospective review of patients identified with p16-positive OPSCC at our institution over a 15-year timeframe.

Materials/Methods: p16-positive immunohistochemistry was used as a surrogate for HPV-associated OPSCC. Patients were categorized according to year of diagnosis (2002-2010 versus 2011-2016). Mean age and proportion of patients over age 65 were statistically evaluated and compared.

Results: From 2002 to 2010, 100 patients were identified with p16-positive OPSCC, mean age at diagnosis was 55.2, and the proportion of patients over 65 was 10.0%. From 2011 to 2016, 188 patients were identified with p16-positive OPSCC, mean age was 58.5, and the proportion of patients over 65 was 19.6%. Both the mean age difference and the difference in proportion of patients over 65 were statistically significant (P = .001 and P = .034, respectively).

Conclusion: The mean age at diagnosis and proportion of patients over 65 has increased over the past 15 years at our institution. This data suggests that HPV-associated OPSCC is being diagnosed more frequently in older persons and that the age demographic may be shifting. Confirmation of this trend with larger patient numbers on a national level will be valuable. This study highlights the importance of maintaining a high clinical suspicion for HPV-associated OPSCC regardless of patient age.

Key Words: HPV, oropharyngeal squamous cell carcinoma, P16-positive, demographics, age.

Level of evidence: 4

INTRODUCTION

The oropharynx is an increasingly common site for presentation of squamous cell carcinoma of the head and neck. Although oropharyngeal squamous cell carcinoma (OPSCC) has been classically associated with tobacco and alcohol consumption,[1] HPV has been recognized as an important cause over the past decade. On the order of 70% to 80% of oropharyngeal cancers are now estimated to be HPV-associated,[2] and the incidence of HPV-associated OPSCC is predicted to continue to increase.[3,4]

HPV-associated OPSCC is significantly different than HPV-negative OPSCC with respect to risk factor profiles, incidence, prognostic considerations, and demographics. Risk factors for HPV-associated OPSCC are related to sexual behavior.[5] The incidence of HPV-associated OPSCC is increasing significantly,[4] and survival rates are notably higher when compared to HPV-negative OPSCC.[6–8] HPV-positive patients are more likely to be male, white, and have a higher socioeconomic status.[3,9,10] In most studies, patient age is about 4 to 8 years younger compared to HPV-negative patients, with median age in the early-mid 50s.[2,11–14]

Over the past decade, studies investigating HPV-associated OPSCC have reported the mean or median patient ages, and these data suggest a possible trend of increasing age. An early study with 40 p16-positive patients from 1988 to 1995 reported a mean age of 50.2 years.[10] Median age in a study of 100 patients from 2000 to 2006 was 54 years,[9] another study of 206 patients from 2002 to 2005 had a median age of 53.5 years,[13] and one-third of 106 patients from 2002 to 2005 had a median age of 54 years.[15] More recently, a study investigating HPV and cancer risk among long-term sexual partners enrolled 164 p16-positive patients between 2009 and 2013 with a median age of 56 years,[16] and the E1308 trial spanning 2010 to 2011 reported a median age of 57 years for 80 patients.[17] Although these are distinct clinical studies with patients from different institutions and geographic areas, these suggest the possibility that the age of this HPV-associated population could be increasing.

In this study, we evaluated demographic changes over the past 15 years for patients identified with p16-positive OPSCC at our institution. We hypothesized that HPV-associated OPSCC is being diagnosed more frequently in older patients, thus gradually increasing the mean age at diagnosis. This could provide insight into a changing patient demographic, and raise awareness of consideration of HPV-associated disease in older patients.

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METHODS

We obtained institutional review board (IRB) approval to analyze the medical records of all patients identified with p16-positive OPSCC at the University of Wisconsin between 2002 and 2016. Our head and neck cancer database was used to identify this population of patients and a retrospective chart review was performed to collect age of diagnosis, year of diagnosis, sex, race, smoking status, primary tumor site, T stage, and overall stage.

The patients were separated into two groups based on diagnosis in 2010 or earlier and diagnosis in 2011 or later. This specific time division was chosen to incorporate a sufficient sample size (100 patients) in the first group while still capturing an adequate time frame (6 years) in the second group. Mean age at diagnosis and standard deviation were calculated for each group, a two-sample F-test for variances was performed to confirm equal variance between groups, and then the difference in mean age between the two groups was evaluated with a two-sample t-test. Mean age was used instead of median to allow for the use of the above mentioned statistical tests. Patients over 65 years old were defined as elderly patients, and the proportion of patients over 65 was evaluated using a two-sample Z-test for proportions. A significance level of $\alpha = 0.05$ was used for all tests. Finally, to evaluate for an age trend over time, the data was further subdivided into a pre-2009 group and four-year periods of 2009 to 2012 and 2013 to 2016. These time period groups were chosen because any further subdivisions to periods less than four years resulted in insufficient sample sizes for any meaningful comparison.

RESULTS

Between 2002 and 2016, a total of 288 patients were identified with p16-positive OPSCC. From 2002 to 2010, 100 patients were identified with p16-positive OPSCC, mean age at diagnosis was 55.2 ± 8.3, and the proportion of patients over 65 was 10.0%. From 2011 to 2016, 188 patients were identified with p16-positive OPSCC, mean age was 58.5 ± 8.6, and the proportion of patients over 65 was 19.6%. Both the mean age difference and the difference in proportion of patients over 65 were statistically significant ($P = .001$ and $P = .034$, respectively). This data is presented in Table I.

Additional demographics, smoking history, and staging data were also collected and compared between groups (Table I). Male to female ratio was 6.7 to 1 for the first group and similar at 7.2 to 1 for the second group. Race was predominantly white for both groups (99.0% and 97.9%). The proportion of patients who were nonsmokers was lower in the first group (31.0% vs. 35.6%), but this difference was not significant ($P = .428$). The proportion of patients who had a smoking history of greater than or equal to 15 pack years was higher in the first group (50.0% vs. 43.1%), but this was also not significantly different ($P = .262$). The distribution of primary tumor site, T stage, and overall stage were similar between the two groups, and this data is also presented in Table I.

TABLE I.
Patient Data at Time of Diagnosis for Time Periods 2002–2010 and 2011–2016.

Year of diagnosis	2002–2010	2011–2016
Number of patients	100	188
Mean age and SD	55.2 ± 8.3	58.5 ± 8.6
Percentage of patients > 65 years old	10.0% (10)	19.6% (37)
Male to female ratio	6.7:1	7.2:1
Race	White - 99.0% (99)	White - 97.9% (184)
	Non-white - 1.0% (1)	Non-white - 2.1% (4)
Smoking status	Nonsmoker - 31.0% (31)	Nonsmoker - 35.6% (67)
	< 15 pack years - 19.0% (19)	< 15 pack years - 21.3% (40)
	≥ 15 pack years - 50.0% (50)	≥ 15 pack years - 43.1% (81)
Primary tumor site	Tonsil - 48.0% (48)	Tonsil - 54.3% (102)
	BOT - 50.0% (50)	BOT - 39.8% (75)
	Soft Palate - 1.0% (1)	Soft Palate - 1.1% (2)
	Unspecified - 1.0% (1)	Unspecified - 4.8% (9)
T stage	T1 - 32.0% (32)	T1 - 27.1% (51)
	T2 - 49.0% (49)	T2 - 42.5% (80)
	T3 - 10.0% (10)	T3 - 12.8% (24)
	T4 - 9.0% (9)	T4 - 17.6% (33)
Overall stage	Stage I - 2.0% (2)	Stage I - 1.6% (3)
	Stage II - 3.0% (3)	Stage II - 2.1% (4)
	Stage III - 8.0% (8)	Stage III - 12.2% (23)
	Stage IV - 87.0% (87)	Stage IV - 84.0% (158)

BOT = base of tongue; SD = standard deviation. Data presented in percentage followed by number of patients in parenthesis.

Data was also subdivided into a pre-2009 group and four-year periods of 2009 to 2012 and 2013 to 2016 to illustrate a trend over time. This data is presented in Table II and Figure 1.

DISCUSSION

We evaluated all patients identified with p16-positive OPSCC at our institution over the past 15 years to investigate for changes in mean age at diagnosis over time. For the time periods of 2002 to 2010 versus 2011 to 2016, there was a statistically significant increase in mean age from 55.2 years to 58.5 years ($P = .001$). This suggests a shift in age in the recent patient population of patients with HPV-associated OPSCC, and this appears to be a gradual

TABLE II.
Demographic Data for the Three Time Period Analysis.

Year of diagnosis	Number of patients	Mean age and SD at time of diagnosis	Percent of patients > 65 years old
Pre–2009	64	55.0 ± 8.8	9.4%
2009–2012	99	56.5 ± 8.9	16.2%
2013–2016	125	59.3 ± 7.9	20%

SD = standard deviation.

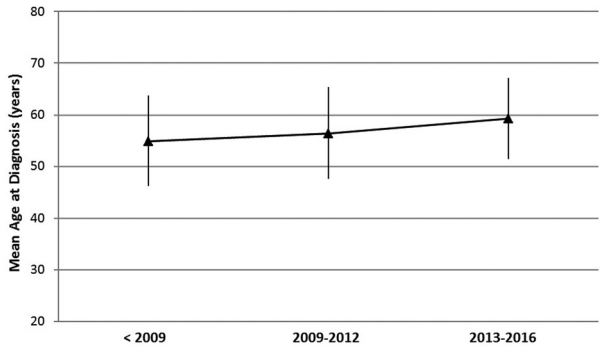

Fig. 1. Mean age at diagnosis over time.

change over the past several years as illustrated by the trend in Figure 1. This change in age did not appear to be accompanied by any changes in other factors such as sex, race, smoking status, primary tumor site, T stage, or overall stage, as these factors remained similar across the compared groups.

Additionally, the proportion of patients over 65 nearly doubled from 10.0% to 19.6%, which was a significant increase (P =.034). HPV-associated OPSCC has classically been considered a disease seen most commonly in middle-aged patients in their 50s.[2,14] This change in the proportion of patients over 65 demonstrates that in recent years, this disease is being diagnosed more frequently in older individuals at our institution. Thus, it is valuable to maintain a high level of suspicion for HPV-associated disease in older patients, and this highlights the importance of ensuring that all oropharyngeal cancer biopsies are tested for p16 status regardless of patient age. HPV tumor status is the strongest independent prognostic factor for oropharyngeal cancer,[18,19] making it important that this testing be performed in all patients with oropharyngeal carcinoma.

There are several potential explanations for why these demographic changes are being observed. We know that there is a long latency period (approximately 10 to 30 years) between exposure to HPV and the subsequent developing of oropharyngeal cancer.[20] It is possible that a change in risk factor profiles related to sexual behavior have been shifting over the past 10 to 30 years and we are now gradually seeing the resulting increase in cancer incidence for the current older patient population. Another possible explanation related to risk factors could be a decline in tobacco use, which may decrease the proportion of tobacco-related malignancies and in turn increase the proportion of HPV-associated malignancies. In this study we did observe a decrease in the proportion of patients with a 15+ pack-year smoking history over time, and although this was not a statistically significant difference it could be clinically significant. Finally, one additional explanation could be a cohort effect related to the baby boomer generation, and as this relatively populous generation ages it could contribute to a gradual increase in the mean age of oropharyngeal cancer diagnosis.

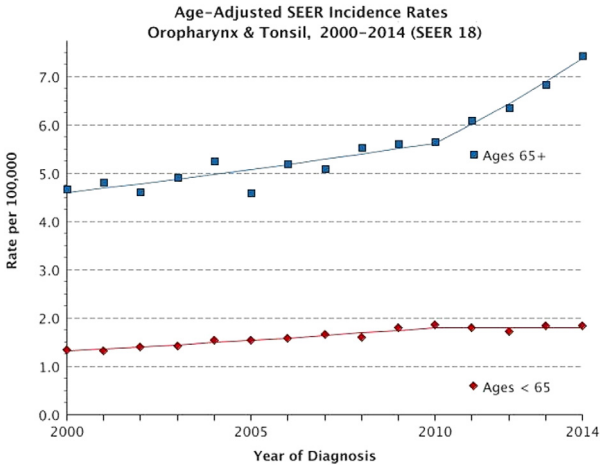

Fig. 2. SEER 18 data for incidence of oropharyngeal carcinoma over time. (https://seer.cancer.gov/faststats)

A limitation of this study is that this data derives from a single institution review. Although there was a statistically significant change in our patient population, this may not reflect changes on the national level, and further study with larger sample sizes will be required to confirm this trend. However, there is some geographically widespread data which suggests that this shift in age demographic could be occurring, such as the trend of mean and median age increase reported in the HPV-associated studies outlined in the introduction (which compares similarly to the mean ages reported in this study adjusted for the appropriate time periods). Additionally, the SEER 18 registry reported an increase in oropharyngeal carcinoma incidence in patients aged 65 and older from a rate of 4.68 per 100,000 in 2000 to 7.45 per 100,000 in 2014, an increase of 59.2%. This is much greater than the 35.6% increase seen in patients less than 65 years old (incidence rate of 1.35 per 100,000 in 2000 to 1.83 per 100,000 in 2014). This data is presented in Figure 2. Although the data from the SEER database includes all patients with oropharyngeal carcinoma and not only HPV-associated OPSCC, this increase is likely driven by the HPV-associated population since it is responsible for 70% to 80% of current oropharyngeal carcinomas and we know that tobacco- and alcohol-related head and neck malignancy is on the decline.[2] This non-HPV-specific SEER data has been similarly used by other studies[20] to demonstrate how the incidence of OPSCC will continue to rise in patients born after 1940 beyond the age of 70.

Another limitation of this study is that p16 staining was not routinely performed at our institution before 2011. Prior to this, p16 staining was less frequent, and many of the pre-2011 specimens were retrospectively stained and analyzed in recent years. Therefore, not all patients with p16-positive OPSCC from pre-2011 were likely captured in this review, and this limits the sample size for the pre-2011 group. There are many examples in head and neck oncology where treatment era may prove confounding (for example, IMRT impact on outcome[21]) and thus care in comparing different eras is always warranted.

CONCLUSION

This work describes the demographics of HPV-associated OPSCC seen at our institution over the past 15 years. It appears that the mean age at diagnosis and proportion of patients over 65 have increased over time. This initial data suggests that HPV-associated OPSCC is being diagnosed more commonly in older persons and that the age demographic may be shifting. Confirmation of this trend with larger patient numbers on a national level will be valuable. This study highlights the importance of maintaining a high clinical concern for HPV status in OPSCC patients regardless of their age.

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