Oropharyngeal Carcinoma in Young Adults: An Alarming National Trend

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Abstract

Objectives. To assess the incidence, treatment methods, and outcomes of oropharyngeal squamous cell carcinoma (OPSCC) in patients younger than 45 years.

Study Design. Retrospective population based.

Setting. Surveillance Epidemiology End Results (SEER) 9 database.

Subjects and Methods. The SEER 9 database was queried from 1973 to 2009 for OPSCC patients <45 years of age.

Results. There were 1603 patients with OPSCC younger than 45 years. The incidence in patients between 36 and 44 years increased from 0.79 to 1.39 (per 100,000). In the same time period, there was an increase in the rate from 0.20 to 0.42 in whites and a decrease in the rate in African American (AA) patients from 0.67 to 0.32. The proportion of grade III/IV tumors also steadily increased from 28% in 1973 to 1979 to 43% in 2000 to 2009 (P < .0001). Surgery alone was performed in 220 patients (13.72%) and in combination with radiation therapy in 734 patients (45.79%). Five-year survival for the study cohort is 54%. Compared with white patients, AA patients had worse survival (P < .0001). Patients who had surgery, either alone (localized stage patients) or in combination with radiation, had the highest 5-year survival followed by those who had radiation.

Conclusions. There was an increase in OPSCC in the study patients within the past 4 decades, particularly in those aged 36 to 44 years. Interestingly, the incidence in whites increased and in AA patients it decreased. It is important to note that most of these patients were treated with surgery, either alone or with radiation therapy. The rising incidence within recent decades is thought to be related to human papillomavirus transmission and changes in sexual practices.

Keywords
orpharyngeal cancer, young adults, SEER database

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Oropharyngeal squamous cell carcinoma (OPSCC) has attained epidemic proportions in the past few years. It is estimated that there will be 13,930 new cases of pharyngeal cancers diagnosed in the United States in 2013.1 The incidence has increased significantly in the 50- to 60-year age group, and high-risk human papillomavirus (HPV) has emerged as a causative and prognostic factor for these cancers.2-4 It has been postulated that the sexual revolution of the 1960s and 1970s led to increased transmission and infection of high-risk HPV.5-8 People who were probably exposed at a younger age are likely now presenting with HPV-positive OPSCC. They have been noted to have a different natural history, clinical behavior, and outcome as compared with HPV-negative counterparts.9

Smoking and alcohol use still remain the most prominent risk factors for OPSCC, similar to other head and neck malignancies.10 It is considered that the effect of numerous risk factors is multiplicative rather than additive for the development of these cancers.10,11 As the rates of tobacco use have been decreasing, the rate of oral cavity cancers declined by 1.9% annually between 1974 and 2004. Meanwhile, base-of-tongue (BOT) and tonsil cancers have increased annually by a rate of 1.3% and 0.6%, respectively.12 The net effect on the incidence trends of OPSCC can be attributed to a decrease in tobacco use over the past several decades and to an increase in HPV infection in a specific subgroup of younger adults. Similar to cervical and anal cancer, it is found that high-risk sexual activity can be considered a risk factor for HPV-positive OPSCC.5,13

The objective of this study is to examine the incidence and treatment trends of OPSCC among patients younger than 45 years at the time of diagnosis using the Surveillance,
Epidemiology, and End Results (SEER) database from 1973 to 2009. We also wanted to investigate whether there are trend differences between races and genders over the past few decades.

**Methods**

Data were obtained from the National Cancer Institute’s SEER program. The SEER program collects cancer incidence and mortality data from several population-based cancer registries covering approximately 28% of the US population. SEER*Stat is a free program provided by SEER to access and analyze information in the research database. Using SEER*Stat, the SEER 9 database was queried for the years 1973 to 2009 to identify patients younger than 45 years with a diagnosis of OPSCC. SEER 9 data are generally representative of the US population as a whole. OPSCC was defined using primary site codes C01.9, C05.1-05.2, C09.0-0.9.1, C09.8-09.9, and C10.0-10.9 and histology codes 8010, 8020, 8070-8074, and 8082-8083.

Inclusion criteria for the study included patients with historically confirmed OPSCC diagnosed between January 1973 and December 2009. The public-use SEER database, which contains only aggregated de-identified data, was used for this analysis, and an institutional review board approval was not required.

Study variables included patient demographics, tumor factors, treatment factors, and survival outcome. Temporal trends by decade (1973-1979, 1980-1989, 1990-1999, 2000-2009) for the diagnosis of OPSCC were evaluated for race, age at diagnosis (less than 35 versus 35-44 years), histologic grade, and SEER summary stage (local, regional, or metastatic). In addition, treatment trends by decade were evaluated for the receipt of surgery or radiation therapy. A combined treatment variable was created to look at the receipt of surgery only, radiation therapy alone, or the receipt of both radiation and surgery. Five-year overall survival was illustrated for all patients using the Kaplan-Meier method and compared with the log-rank test. Differences in 5-year survival were compared by sex, race, treatment, and age group. Racial differences in 5-year survival were further stratified by decade.

Rate sessions in SEER*Stat were run to generate age-adjusted rates and trends for OPSCC. Age-adjusted rates for each year were plotted stratified by age group, sex, race, and sex and race combined. Rates were age adjusted to the 2000 US Census population standard. Finally, a MIP-SIRs (multiple primary, standardized incidence ratios) session was run to look at the occurrence of cancers diagnosed after the OPSCC diagnosis. Standard incidence ratios (SIRs) were calculated overall and for 4 latency periods (2-11 months, 12-59 months, 60-119 months, and 120 months or longer). HPV data are not available in the SEER database. We therefore used higher tumor grade (III/IV) as a surrogate marker for HPV positivity instead. A 2-sided $P$ value less than .05 was considered statistically significant, and statistical analyses were conducted using SAS 9.2 software (SAS Institute, Cary, NC) and SEER*Stat.

**Results**

According to our inclusion and exclusion criteria, a total of 1603 patients with OPSCC were included in this analysis. Table 1 highlights the patient characteristics with respect to race, gender, age group, histologic grade, and SEER stage. There has been a significant increasing trend in OPSCC in patients younger than 45 years, specifically within the subgroup of patients aged 35 to 44 years. Rates increased overall for these young patients from 0.23 to 0.37 per 100,000 population between 1973 and 2009. The incidence for the subgroup of patients 35 to 44 years has increased from 0.79 to 1.39 (per 100,000) during the same time period (Figures 1 and 2). Over the same time period, the rates were steady for those younger than 35 years.

Significant trends were also noted with regard to race. Most patients were white (73%), and there was an increase in the rate of white patients from 0.20 to 0.42 per 100,000 over this time period. Meanwhile, the rate of young African American (AA) patients declined from 0.67 to 0.32 per 100,000 (Figure 3).

Regarding gender, there were increased rates in men from 0.27 to 0.57 from 1973 to 2009. Meanwhile, there was no significant change in rates in women as they remained about 0.18 to 0.17 per 100,000. On further subgroup analysis, the most evident increase in rates was noted among white men (Figure 3).

A steady increase in the rates of poorly differentiated histology (grade III/IV) was noted from 28% in 1973-1979 to 43% in 2000-2009 ($P < .0001$; Table 1). With regard to stage, there has also been a decrease in local (T1-4N0M0 disease) and metastatic OPSCC, while regional stage (node positive) has increased from 49% in 1973-1979 to 72% in recent years ($P = .02$).

Examination of treatments offered to patients as recorded in the SEER 9 database revealed that most of these younger patients (50%-65% during different time periods) have had surgical resection for their tumors. The percentage of patients undergoing surgery was 51% from 1973-1979, 59.6% from 1980-1989, 67.8% from 1990-1999, and 58.3% from 2000-2009 (Table 2). Patients with local stage disease were more likely to undergo surgery as opposed to regional or distant stages (Table 3). Details regarding the type of surgery have been better classified since 1988 as recorded in the SEER database. From 1988-1997, the most commonly reported surgical procedure was a local/radical excision with radical neck dissection. From 1998-2009, the most commonly reported surgical procedure was a pharyngectomy/tonsillectomy, as recorded by the SEER database.

Five-year survival for the entire study cohort is 54%. Compared with white patients, AA patients had worse survival ($P < .0001$; Figure 4b). The mean survival times for white patients were 34.3, 42.4, 47.2, and 50.1 months for the years 1973-1979, 1980-1989, 1990-1999, and 2000-2009, respectively. The mean survival times for AA patients were 16.7, 26.4, 30.3, and 29.9 months for the years 1973-1979, 1980-1989, 1990-1999, and 2000-2009, respectively. Patients who
had both surgery and radiation had the highest 5-year survival, followed by surgery alone and radiation alone (P < .0001; Figure 4c). No significant differences in survival were noted between genders or age groups (Figures 4a, 4d).

A total of 200 (12.5%) second primary malignancies were noted in these 1603 patients. Most of these were in the oral cavity and pharynx (n = 69), lung and bronchus (n = 44), and esophagus (n = 18; Table 4). Patients with OPSCC were more than 4 times more likely to develop a secondary cancer than the regular US population (SIR, 4.21; 95% confidence interval [CI], 3.65-4.83).

Discussion

The incidence of OPSCC in the United States has increased in recent decades.17 Our SEER database analysis also revealed this alarming trend in the younger (<45 years old) population. A significant increase in OPSCC was noted between the years 1973 and 2009.

Racial and gender differences exist for these incidence trends. With regard to race, AA patients have higher rates of oral cavity and oropharyngeal cancers compared with other races.18,19 This is interesting, as we noted that within the subgroup of younger adults with OPSCC, the rates are decreasing in AA patients and increasing in white patients. Regarding gender, most patients with head and neck squamous cell cancer are men.18,20 The rate of OPSCC has been increasing among men while it has been decreasing among women in the United States in recent decades.17 It has also previously been shown that there has been a more significant increase in the rates of men younger than 50 years between 1980-1990 and 1991-2001.17

An examination of the stage and grade of tumor at presentation revealed that the rate of grade III/IV OPSCC in young adults has steadily increased over the past 3 decades.
This correlates with data that show that there has been an increase in more poorly differentiated tumors for all comers with OPSCC. It is reported that adults with OPSCC more commonly present with more regionally staged (node-positive) disease. This is consistent with what we observed; among young adults, there has been a decrease in local stage and metastatic stage OPSCC, while regional stage OPSCC has increased in recent years.

We noted 200 second primary malignancies among these 1603 young adult patients. Most of these were noted to arise

Figure 2. Incidence trends based on age groups: (a) age 0 to 34 years; (b) ages 35 to 44 years.

Figure 3. Incidence trends by race and gender showing a steady increase in incidence among white men. Rates in (a) white men, (b) African American men, (c) white women, and (d) African American women.
in the oral cavity, pharynx, and lungs. Based on available data, it is not possible to determine if these secondary malignancies were in the radiation field for these patients. Radiation therapy is a known risk factor for the development of secondary malignancies within the radiation field in patients treated with head and neck cancers. Most secondary malignancies in adults treated for head and neck cancers develop in the aerodigestive tract. Survival analyses show inferior outcomes for young AA patients with OPSCC. This is consistent with data showing worse survival for AA patients of all ages with head and neck SCC. There has been an improvement in median survival seen over the decades for young adult OPSCC. However, disparity between races has remained consistent. No survival difference was present between genders in our study. Patients who underwent both surgery and radiation had the highest 5-year survival followed by surgery alone and radiation alone. This is consistent with previous data for all ages, as the Eastern Cooperative Oncology Group (ECOG) 2399 showed benefit to survival for OPSCC patients who underwent multimodality treatment. It is likely that those treated with surgery alone had earlier stage cancers.

One of the limitations of this analysis is that the SEER database does not record information regarding chemotherapy, substance abuse (smoking and alcohol abuse), comorbidities, or HPV status. We therefore regarded higher tumor grade (III/IV) as a surrogate marker for HPV positivity. HPV-positive SCC has been shown to be correlated with basaloid and poorly differentiated SCC on pathologic review.

The study of young adults with this disease warrants further investigation and research. It has been shown previously that HPV is becoming prevalent in young adults. However, there is much that still remains unanswered with regard to HPV status and its effect on OPSCC. A theory for the rise of HPV-positive OPSCC, especially among young adults, is exposure to risky sexual practices that became

### Table 2. Treatment trends by decades.

<table>
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<tr>
<td><strong>All years</strong></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td><strong>Total</strong></td>
<td>1603</td>
<td>149</td>
<td>354</td>
<td>513</td>
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<td></td>
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<tr>
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<td>568</td>
<td>57</td>
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<td>159</td>
<td>232</td>
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<td>977</td>
<td>76</td>
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<td>58</td>
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<td>23</td>
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<tr>
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<td>38</td>
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<td>69</td>
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<td>1266</td>
<td>106</td>
<td>242</td>
<td>409</td>
<td>509</td>
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<td>Unknown</td>
<td>49</td>
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<td>19</td>
<td>16</td>
<td>9</td>
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<td><strong>Combined treatment</strong></td>
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<td>15</td>
<td>25</td>
<td>12</td>
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<td>28</td>
<td>75</td>
<td>63</td>
<td>54</td>
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<td>488</td>
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<td>97</td>
<td>128</td>
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<td>129</td>
<td>276</td>
<td>283</td>
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<td>20</td>
<td>38</td>
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### Table 3. Treatment details by SEER stage.

<table>
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<tr>
<th>SEER stage</th>
<th>Local</th>
<th>Regional</th>
<th>Distant</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td>None</td>
<td>4</td>
<td>2</td>
<td>27</td>
<td>3</td>
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<tr>
<td>Surgery only</td>
<td>102</td>
<td>41</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>Radiation only</td>
<td>46</td>
<td>19</td>
<td>341</td>
<td>32</td>
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<tr>
<td>Both</td>
<td>83</td>
<td>33</td>
<td>548</td>
<td>51</td>
</tr>
<tr>
<td>Unknown</td>
<td>13</td>
<td>5</td>
<td>62</td>
<td>6</td>
</tr>
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</table>
especially predominant during and after the “sexual revolution” in the 1960s in the United States. Patients who likely took part in said sexual revolution would have likely been in their teenage years to their 30s at that time, which would therefore make them in their 50s to 70s today, 50 years later, when they are being diagnosed with OPSCC. Yet, as this SEER database analysis reveals, there is a rise of young adults younger than 45 years with likely HPV-associated OPSCC. Although they were not a part of the sexual revolution of the 1960s, they likely partook in the same risky sexual practices as their elder counterparts. However, this does not explain why they are presenting with disease at an earlier age than the older patients. We speculate that this could potentially be due to several reasons: a decreased latency period from HPV infection to cancer development, infection with a more virulent strain of HPV, or a change in transmission pattern of HPV.

This alarming increase in young adult OPSCC is concerning and has implications for both preventive and screening measures as well as for minimizing the impact of cancer therapy on future quality of life. Campaigns to increase public awareness regarding early cancer detection should be

Table 4. Secondary malignancies by time after treatment.

<table>
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<tr>
<th>Latency periods, mo</th>
<th>Observed</th>
<th>Expected</th>
<th>O/E</th>
<th>CI lower</th>
<th>CI upper</th>
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<td>2-11</td>
<td>18</td>
<td>2.01</td>
<td>8.94</td>
<td>5.3</td>
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<td>12-59</td>
<td>58</td>
<td>8.02</td>
<td>7.23</td>
<td>5.49</td>
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<td>60-119</td>
<td>55</td>
<td>10.02</td>
<td>5.49</td>
<td>4.13</td>
<td>7.14</td>
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<tr>
<td>120+</td>
<td>69</td>
<td>27.47</td>
<td>2.51</td>
<td>1.95</td>
<td>3.18</td>
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Abbreviations: CI, confidence interval; O/E, observed-to-expected ratio.
considered. Some are of the opinion that HPV-positive OPSCC is being overtreated with unnecessary modalities. Current and ongoing trials from cooperative groups that are trying to answer these questions include Radiation Therapy Oncology Group 1016 and ECOG1308. Treatment de-escalation should be studied further in young adults, as these patients are otherwise healthy and likely to live for a long time. This may help in minimizing treatment-related side effects and the risk of secondary malignancies, thus improving quality of life in these patients.

Author Contributions

Omar H. Gayar, analyzed data, wrote article; Julie J. Ruterbusch, collected/analyzed data, revised article; Mohamed Elshaikh, study conception/design, revised article; Michele Cote, collected/analyzed data, revised article; Tamer Ghanem, study conception/design, revised article; Francis Hall, study conception/design, revised article; Farzan Siddiqui, study conception/design, analyzed data, wrote article.

Disclosures

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