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Outcomes of oral cavity squamous cell carcinoma in pediatric patients

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Abstract

Background—Oral cavity squamous cell carcinoma (OCSCC) is uncommon in young patients and rare in the pediatric population. OCSCC is believed to behave aggressively in this age group, but the existing literature is limited to case reports. The objective of this study was to compare survival outcomes in pediatric and adult patients with oral cavity squamous cell carcinoma.

Methods—Population-based study of 54 pediatric (age ≤ 20) and 22,162 adult cases of OCSCC, recorded in the SEER cancer registry. Overall survival (OS) and disease-specific survival (DSS) were analyzed using the Kaplan-Meier method. Cox multivariable regression was used to control for covariates including gender, stage, histologic grade and treatment modality.

Results—Pediatric patients with OCSCC experienced significantly better DSS than adult patients (75.3% vs. 63.5%, $p=0.02$). Pediatric patients were also more likely to be female (37.0% vs. 31.7%, $p=0.04$) and to receive surgery (87.0% vs. 68.6%, $p<0.001$). When these factors, as well as non-significant differences in rates of metastases and histologic grade were controlled for on multivariable analysis, the pediatric and adult groups experienced equivalent DSS ($p=0.64$).

Conclusions—Pediatric patients with OCSCC experience better survival than adult patients. When differences in patient, tumor and treatment-related characteristics are adjusted for, the two groups experience equivalent survival.

Keywords

Pediatric; young; children; adolescent; oral; cavity; squamous cell; carcinoma; cancer

INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is rare in pediatric patients (defined by the American Academy of Pediatrics as patients under age 21), accounting for approximately 1 in 1,000 cases^{1–4}. OCSCC in pediatric patients is believed to be etiologically distinct from adult OCSCC, because the usual risk factors such as tobacco and alcohol exposure are typically absent⁵. However, there is disagreement in the literature regarding outcomes of OCSCC in

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CONFLICTS OF INTEREST

None declared.

pediatric and young patients. Many clinicians believe that this disease is particularly aggressive in young patients, and is associated with poorer survival compared to adults^{3,5-8}. Because of the rarity of OCSCC in pediatric patients, the literature consists entirely of isolated case reports, many of which report poor outcomes^{1,3,8-16}. Much of the opinion regarding OCSCC in this age group has been extrapolated from studies of young adults under 40 years of age^{7,17-22}.

There are two obstacles to analyzing outcomes of OCSCC in the pediatric population: OCSCC is rare in this age group, and clinical reports from referral centers likely represent a selected patient group. Population-based cancer registries record all incident cases within defined geographic areas, and are therefore able to offer larger sample size while minimizing institutional selection bias. The objective of this study was to utilize data from the Surveillance Epidemiology and End Results (SEER) program to compare outcomes of OCSCC of pediatric patients compared to adult patients.

METHODS

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program is considered the gold standard cancer registry, having collected data continuously since 1973 and now capturing 26% of the United States population. The SEER registry collects detailed information on patient demographics, tumor characteristics, and therapy. All patients are followed for vital status in order to permit survival analysis. Quality control is an integral part of the SEER program, and comparison studies have confirmed that pathologic, surgical and radiation data are accurately recorded²³⁻²⁴. However, there are limitations of this dataset compared to large institutional prospective studies. Some clinical details are not recorded, including risk factors such as tobacco use, alcohol use, and human papillomavirus status. Some treatment details such as chemotherapy and the dose of radiation therapy are not recorded. Cancer recurrence is also not recorded. There is no centralized pathology review and pathologic data relies on medical records from the treating institutions. The National Cancer Institute does not require institutional board approval for use of this deidentified dataset.

Using SEER*Stat release 6.5.2 (July 2009; NCI Cancer Statistics Branch, Bethesda, MD), cases were identified using the International Classification of Diseases in Oncology, 3rd edition (ICD-O-3) codes for invasive squamous cell carcinoma (histology codes 8070-8076 and 8078) and subsites of the oral cavity (lip, oral tongue, upper and lower gums, floor of mouth, buccal mucosa, hard palate, retromolar trigone and other mouth). Based upon the American Academy of Pediatrics definition of the pediatric age group, patients aged ≤ 20 years old were identified to form a cohort of 54 patients. Details of gender, histology, tumor grade, subsite of primary tumor, primary tumor size and extent, presentation with regional or distant metastases, scope of surgery at the primary site and neck, timing of radiation therapy, survival time, vital status and cause of death were recorded. An adult cohort of patients aged 21 years old and older was also constructed using the same parameters, selecting patients from the identical diagnosis years of the pediatric patients. This adult cohort included 22,162 adult patients with OCSCC.

The null hypothesis was that overall and disease-specific survival would not differ between pediatric and adult patients. The two groups were compared on univariate analysis consisting of continuous (t-test) and categorical (chi-squared and Fisher exact) statistics. Overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier method, and comparisons made with the two-tailed log-rank test. In order to control for possible differences between pediatric and adult patients in gender, stage of disease, histologic grade, and treatment modality, these covariates were included in a multivariable Cox proportional hazards regression model. This allowed identification of factors independently predictive of disease-specific survival. An adjusted survival curve was then created by entering the mean value of each covariate into the proportional hazards regression equation. The a priori level of

significance was $p=.05$. All analyses were carried out in SPSS v. 17.0 (SPSS, Inc., Chicago, IL).

RESULTS

Between 1973 and 2006, a total of 54 pediatric patients were identified in the SEER registry. The youngest patient was under 1 year old, and there were 5 patients younger than 10 years old. Median followup was 53 months (range 2–391). Tumor subsites included 35 cases (63.6%) of SCC of the oral tongue, followed by the lips (8 cases, 14.5%), upper alveolus (4 cases, 7.2%), lower alveolus (3 cases, 5.4%), buccal mucosa (2 cases, 3.6%), and 1 case (1.9%) each of the hard palate, retromolar trigone, and floor of mouth. One patient experienced 2 separate head and neck primary cancers, of the oral tongue and lips, at ages 11 and 13. An adult cohort of 22,162 cases was also identified, drawn from diagnoses in identical years. Median followup in the adult cohort was 30 months (range 1–407).

Patient and tumor characteristics for the pediatric and adult cohorts are shown in Table 1. On univariate analysis, the pediatric cohort differed from the adult cohort in several respects. Pediatric patients were significantly more likely to be female (37.0% vs. 31.7%, $p=0.04$) and significantly more likely to receive surgical therapy (87.0% vs. 68.6%, $p<0.001$). Other univariate comparisons did not reach statistical significance: pediatric patients were less likely to present with cervical metastases (31.3% vs. 43.7%, $p=0.19$), and more likely to have well differentiated histology (33.3% vs. 21.0%, $p=0.11$). All 5 variables in Table 1 were included in the multivariable analysis.

Overall survival at 5 years was 75.3% in the pediatric cohort and 47.1% in the adult cohort ($p<0.0001$). Disease-specific survival (DSS) at 5 years was 75.3% in the pediatric cohort and 63.5% in the adult cohort ($p=0.02$, Figure 1). Because of the differences in the patient and tumor characteristics of the two groups, a multivariable Cox regression analysis was performed to compare DSS, controlling for differences in gender, stage of disease, histologic grade, and treatment. The multivariable analysis (Table 2) revealed that DSS was independently associated with gender, cervical and distant metastases, histologic grade, and treatment modality. Compared with patients treated with surgery alone, there was an increasing risk of disease-specific death for patients treated with surgery and radiation (HR 1.71), radiation alone (HR 2.47), and patients receiving no treatment (HR 5.90).

DSS was not independently predicted by pediatric or adult age status. Therefore, when other covariates were controlled for, the pediatric and adult cohorts experienced equivalent DSS. The adjusted survival curve of DSS at the mean of the covariates (Figure 2) represents survival for the pediatric and adult cohorts while controlling for differences in gender, stage of disease, histologic grade, and treatment modality. This depiction of DSS demonstrates equivalence of outcomes in the pediatric and adult cohorts ($p=0.64$).

DISCUSSION

Approximately 1 in 1,000 new diagnoses of oral cavity squamous cell carcinoma will occur in pediatric patients¹, rendering this disease entity poorly understood. Because of its rarity, the literature on OCSCC in these young patients is limited entirely to case reports^{1,3,8–16}. Based on the available literature, researchers have argued that OCSCC in the pediatric and young adult population behaves more aggressively, and carries a worse prognosis^{3,5–8}. However, it is unknown whether these case reports accurately reflect the natural history of pediatric OCSCC, or whether cases with poor outcome are over-represented in the literature.

Explanations for the apparent poorer prognosis in young patients include differences in etiology and delay in diagnosis. In the first case, the usual risk factors for SCC (tobacco and alcohol)

are either absent or present only for limited duration. In some cases, the contributing risk factor might be a genetic syndrome such as Fanconi Anemia, xeroderma pigmentosum, keratosis-ichthyosis-deafness (KID) syndrome^{11,14-15}, or an as-yet unidentified genetic risk factor. Less common would be a secondary malignancy following chemotherapy or radiotherapy. Delay in diagnosis has also been cited as a cause for poorer outcome in young patients⁸. A malignancy may not be initially suspected in young patients, and a biopsy may not be performed in a timely fashion, possibly leading to poorer prognosis.

A review of published cases of pediatric OCSCC by Stolk-Liefferink et al included 65 patients under 21 years of age, and 4 patients under 12 years of age⁸. However, most reports included few or no clinical details. To date, low numbers of incident cases have precluded systematic reviews of outcomes in pediatric OCSCC.

The assumption of poor prognosis in pediatric patients has been extrapolated from several anecdotal case reports of aggressive disease, and from the more extensive outcomes literature on young adults (ages 20–40) with OCSCC. However, there is disagreement in the literature regarding outcomes in young adults with OCSCC. A number of retrospective reviews in the 1970s and 1980s reported poor outcomes in young adults^{7,25-27}. A meta-analysis of 14 studies published in 1994 reported that, despite a tendency to present at an earlier stage of disease, young adult patients experienced high rates of locoregional recurrence (57%) and disease-specific mortality (47%)⁷. Accordingly, many authors initially urged more aggressive surgery and radiotherapy in young patients. However, these early reports were based on studies with small sample sizes and comparisons with historical control data²². It is also likely that publication bias may have led to a predominance of early reports of poor outcomes in young patients.

In order to address these limitations, Friedlander and colleagues at Memorial Sloan-Kettering Cancer Center carried out a matched-pair analysis of oral tongue SCC in young adults, matching 36 young adult patients (under 40 years old) to 36 patients between 60 and 70 years old. Disease-specific survival in the two groups was equivalent¹⁷. More recent studies by Funk et al utilizing the National Cancer Database²⁰ and Davidson et al, using the SEER program¹⁸, as well as three other institutional studies²⁸⁻³⁰, have consistently reported that younger adults with oral cavity SCC experience similar or better disease-specific survival than older adults. Recently, Goldenberg et al utilized data from the SEER program to compare young adult patients (ages 18–40) to older adult patients (age older than 40), adjusting for patient and disease characteristics such as gender, race, subsite and stage. Disease-specific survival was significantly better in younger patients, although treatment modality was not controlled for³¹. If older patients are less likely to receive cancer-directed surgery, this may explain poorer outcomes in older patients.

In fact, adult patients in our study were significantly less likely to receive surgery and more likely to receive radiation alone. On multivariable analysis, treatment with radiation alone was independently associated with a higher risk of disease-specific death (OR 2.47, $p < 0.0001$), compared to surgery or surgery and radiation. These results suggest that, in patients with oral cavity cancer, treatment with radiation leads to poorer survival than surgical resection. However, much of this difference is likely attributable to the presence of high-risk patients in the radiation treatment group who were unable to receive surgery due to unresectable disease or medical comorbidity.

In the present study, outcomes in pediatric and adult patients with oral cavity SCC were compared. We chose 20 years as our upper age limit based on the American Academy of Pediatrics definition of the pediatric age group³². This has also been the lower age limit of most studies focusing on young adults. Analysis was limited to the oral cavity, rather than all

head and neck mucosal sites, in order to limit heterogeneity of disease and because oncogenic human papillomavirus is uncommon in oral cavity cancers³³.

In this study, disease-specific survival for the pediatric cohort was significantly better than for the adult cohort. However, there were differences between pediatric patients and adult patients in gender distribution and in rates of cervical metastases, high-grade histology, and treatment with surgery. Each of these factors was independently associated with survival. After adjusting for these differences on multivariable analysis, disease-specific survival was identical in the pediatric and adult cohorts.

Weaknesses of this study include the limitations of cancer registries. As described in the Methods section, data from the SEER program is accurate, but does not include some details such as risk factors (smoking, tobacco, human papillomavirus), treatment with chemotherapy, and recurrence outcomes. Also, there is no centralized pathology review. Nevertheless, for cancers such as pediatric OCSCC, no institutional studies have been possible due to low incidence. SEER registry data offer the advantage of population-based data, which reduces institutional referral or selection biases. We note that median follow-up time in the adult cohort was shorter than in the pediatric cohort. This was likely due to higher rates of both cancer-specific and competing causes of mortality in the older adult population.

Oral cavity squamous cell carcinoma is exceedingly rare in children and adolescents, and poses special challenges for parents and physicians due to the emotional aspects and technical challenges of safe oncologic resection in these young patients. Nevertheless, we believe that the preponderance of case reports of aggressive disease and poor outcome in pediatric patients is not an accurate reflection of true outcomes. To the contrary, evidence from the SEER cancer registry demonstrates that pediatric OCSCC patients experience better survival outcomes than adults. When pertinent differences in stage, grade and treatment are controlled for, outcomes are equivalent.

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Figure 1. Disease-specific survival for pediatric and adult cohorts

Disease-specific survival for pediatric patients was significantly better than for adult patients.

Figure 2. Adjusted disease-specific survival (controlling for covariates) for pediatric and adult cohorts

Disease-specific survival was adjusted for differences in gender, stage, grade and treatment by plotting survival at the mean of these covariates for both cohorts.

Table 1

Patient and tumor characteristics: pediatric (under age 20) and adult cohorts.

Age			
0–4	2 (3.0%)	-	<.0001
5–8	2 (3.0%)	-	
9–12	3 (4.5%)	-	
13–16	9 (13.6%)	-	
17–20	38 (57.6%)	-	
21–40	-	876 (4%)	
41–60	-	8182 (36.9%)	
>60	-	13096 (59.1%)	
Gender			
Male	34 (63.0%)	15137 (68.3%)	0.041
Female	20 (37.0%)	7025 (31.7%)	
Stage			
N0	29 (60.4%)	10616 (47.9%)	0.19
N+	15 (31.3%)	9685 (43.7%)	
DM	4 (8.3%)	1862 (8.4%)	
Treatment modality			
Surgery alone	27 (50.0%)	9790 (44.2%)	<0.001
Surgery + RT	20 (37.0%)	5454 (24.6%)	
RT alone	0	5073 (22.9%)	
No treatment	7 (13.0%)	1845 (8.3%)	
Histologic grade			
Well differentiated	18 (33.3%)	4654 (21.0%)	0.11
Moderately differentiated	20 (37.0%)	9042 (40.8%)	
Poorly differentiated	6 (11.1%)	4144 (18.7%)	
Undifferentiated	0	133 (0.6%)	

N0, node negative. N+, node positive. DM, distant metastases. RT, radiation therapy.

Table 2

Factors predictive of disease-specific survival.

Age cohort		
Pediatric	0.86 (0.46–1.60)	0.64
Adult		
Gender		
Female	1.24 (1.18–1.30)	<.0001
Male		
Extent of disease		
N0	referent	
N+	2.10 (1.97–2.25)	<.0001
DM	3.73 (3.42–4.06)	<.0001
Histologic grade		
Well differentiated	referent	
Moderately differentiated	1.11 (1.03–1.21)	0.005
Poorly differentiated	1.10 (1.01–1.19)	0.03
Undifferentiated	1.03 (0.83–1.28)	0.80
Treatment modality		
Surgery alone	referent	
Surgery + RT	1.71 (1.58–1.84)	<.0001
RT alone	2.47 (2.28–2.67)	<.0001
No treatment	5.90 (5.33–6.52)	<.0001

N0, node negative. N+, node positive. DM, distant metastases. RT, radiation therapy.