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Oral tongue carcinoma among young patients: An analysis of risk factors and survival

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ABSTRACT

Introduction: The incidence of oral tongue squamous cell carcinoma (OTSCC) in younger adults has rapidly increased over the past two decades. While tobacco and alcohol use may be less likely to cause these tumors, it remains controversial whether differences also exist in their prognosis. Our aim is to examine the risk factors for cancer among young (< 45 years old) OTSCC patients at our institution, and to compare their recurrence and survival with older patients in a matched cohort.

Materials and methods: All OTSCC patients seen at our institution between 2000 and 2015 were reviewed. Patients under 45 who with sufficient treatment information were matched 1:1 on race, T-stage, and N-stage with patients 45 and older. Three-year recurrence and survival were determined in stratified and adjusted Cox regression models.

Results: Of 397 OTSCC patients were seen at our institution, 117 (29%) were less than 45 years old. Younger patients were significantly more likely to be female, (50% vs. 39%; $p = 0.04$) and to abstain from tobacco (51% vs. 39%; $p < 0.01$). Young patients in the matched cohort were significantly more likely to have a recurrence (HR 3.9 95% CI 1.4–10.5). There was no difference in overall survival.

Conclusion: Younger OTSCC patients in a matched cohort were more likely to recur within 3 years, although there was no difference in overall mortality. Differences in risk factors and recurrence between older and younger patients suggest that some cancer among younger patients may be distinct from traditional OTSCC.

Introduction

Every ear, approximately 11 in 100,000 adults in the United States are diagnosed with oral cavity cancer [1]. Oral tongue squamous cell carcinoma (OTSCC) is a common and often lethal form of this disease. OTSCC was traditionally thought to affect men in their 60s and older, after extensive tobacco and alcohol use [2–5]. Over the past two decades OTSCC incidence has declined in this population due to improved awareness of tobacco-associated risks. However, studies have noted an alarming increase in OTSCC among of young patients, especially white women, over this same time period [6–10]. Between 1975 and 2007, there was a 44% increase in OTSCC incidence among white men under the age of 44, and a 111% increase among young women [7]. While several studies have demonstrated similar trends, the etiology of this increase in incidence remains unknown [7–9].

Previous data suggests that younger patients are less likely to have a history of significant tobacco or alcohol exposure [11,12]. The absence of these traditional risk factors among young OTSCC patients has been noted globally, in nations including the US, the UK, Italy, India and Brazil [12]. Novel risk factors may play a role in these patients, although none have yet been described aside from a family history of cancer [11–14].

The prognosis in these young patients with OTSCC is controversial. While many studies have found that younger and older OTSCC patients have comparable outcomes when accounting for stage-at-presentation [15,16–21]; most were likely underpowered to detect a difference. Several recent studies have suggested that younger patients may actually have worse recurrence and survival compared to older patients, while another study has suggested that young OTSCC patients may have a propensity for early recurrence [21]. More research is needed to guide prognostic and treatment guidelines.

Our objective in this study is to compare the characteristics of

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younger and older OTSCC patients at our institution. Our first aim is to determine whether there are differences in the risk factors for OTSCC, such as gender and tobacco use. Our second aim is to match younger and older OTSCC patients to examine differences in pathological markers, recurrence and survival in a stage and race-matched cohort. We finally examined the predictors of disease-survival in each age category.

Materials and methods

Population

A retrospective cohort was created using all patients with OTSCC seen at our institution between 2000 and 2015. Patients with distant metastases and patients under the age of 18 were excluded. The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Aim 1: Risk factors for disease

The age, sex, race, tumor stage, prior alcohol history, and prior tobacco history for all OTSCC patients at the time of presentation were extracted from electronic medical records. "Young" OTSCC patients were defined as those less than 45 years old (n = 117), and "Older" OTSCC patients were defined as those 45 or older (n = 283). We examined the risk factors for OTSCC for differences between young and older patients using Chi-squared tests and Fischer's exact tests (if a group contained less than 5 patients).

Aim 2: Survival

For this analysis, we included only patients who were either white or black American, primarily treated at our institution, and had available follow-up data. Patients under 45 were matched 1:1 on race, T-stage and N-stage with patients over 45. For the purpose of matching, T stage was dichotomized into T1-2 and T3-4, and N stage was dichotomized into N0 and N1-3. The 7th edition AJCC criteria were used for staging. Fifty-six patients under 45 both met these criteria and had an equivalent match.

Demographics, stage, comorbidities, and treatments were then compared using chi-squared tests and Fischer's exact tests with < 5 patients in a cell. Recurrence and overall survival was determined using stratified log-rank tests, stratifying on T and N stage, as well as multivariate stratified Cox-proportional hazard models adjusting for sex, tobacco use, and alcohol use, and stratified on T stage, and N stage. Cox-proportional hazard models were finally used to determine the predictors of 3-year disease-free survival in both young and older OTSCC patients, with sex, race, T-stage, N-stage, prior alcohol use, and prior tobacco use (10+ vs. < 10 pack-years) included in the models. The proportional hazards assumption was tested and satisfied for all variables used. All analysis was conducted in Stata 15 (StataCorp, College Station, TX).

Results

Risk factors by age

There were 397 OTSCC patients seen at our institution; 117 (29%) were less than 45 years old and 280 (71%) were older. There were significant differences in gender, tobacco and alcohol use, and stage at presentation between the two age groups (Table 1). Younger OTSCC patients were more likely to be female (50% female vs. 39% for young and older patients respectively; p = 0.042) less likely to use tobacco (49% vs. 69% p < 0.01), and less likely to drink alcohol (34% vs. 47%; p = 0.016). Younger patients were also more likely to present at a lower T-stage (85% vs. 67%; p < 0.01). There was no significant difference by race, and there were no significant differences by N stage.

Table 1
Demographics, behaviors, and stage at presentation for full population.

	Age < 45 *(n = 117)*		Age 45+ *(n = 280)*		P-value
	No.	%	No.	%	
Age category					
< 30 (n = 48)	48	41%			
30–45 (n = 69)	69	59%			
45–60 (n = 132)			132	47%	
60–75 (n = 117)			117	42%	
75+ (n = 31)			31	11%	
Sex					
Male (n = 229)	58	50%	169	61%	0.042
Female (n = 170)	59	50%	110	39%	
Race					
White (n = 304)	90	78%	211	78%	0.849*
Black (n = 45)	6	5%	39	14%	
American Indian (n = 2)	1	1%	1	0%	
Asian (n = 6)	3	3%	3	1%	
Other (n = 20)	11	10%	9	3%	
Not specified (n = 11)	4	3%	7	3%	
Tobacco use					
No tobacco use (n = 146)	59	51%	87	31%	< 0.001
Tobacco use (n = 251)	56	49%	192	69%	
Tobacco type					
Cigarettes (n = 234)	50	43%	181	65%	< 0.001
Cigars (n = 12)	2	2%	10	4%	0.331
Chewing tobacco (n = 18)	8	7%	10	4%	0.147
Tobacco history					
< 10 years (n = 180)	78	69%	101	37%	< 0.001
10+ years (n = 207)	35	31%	170	63%	
Alcohol use					
Non-drinker (n = 223)	102	90%	254	92%	0.021
Drinker (n = 169)	11	10%	22	8%	
Drinks per day					
< 1 drink/day (n = 359)	102	90%	257	92%	0.571
1+ drink/day (n = 33)	11	10%	22	8%	
T stage					
1 (n = 136)	48	42%	88	31%	0.001**
2 (n = 150)	50	43%	100	35%	
3 (n = 62)	13	11%	49	17%	
4 (n = 47)	4	3%	43	15%	
N stage					
0 (n = 237)	74	64%	163	58%	0.340***
1 (n = 45)	12	10%	33	12%	
2 (n = 111)	30	26%	81	29%	
3 (n = 4)	0	0%	4	1%	

* P-value for white vs. non-white.
** P-value for high-stage vs. low stage.
*** P-value for N0 vs. N+.

Survival by age

Out of 56 younger and 56 older patients were matched on age, race, T-stage, and N-stage. Mean ages were 34 and 64 respectively. When comparing risk factors, the younger cohort was again significantly less likely to have used tobacco (55% vs. 36%; p = 0.05). Younger patients were also more likely to have had either perineural invasion (PNI) or lymphovascular invasion (LVI) on pathology (36% vs. 18%; p = 0.04), and to have received adjuvant treatments in addition to primary surgery (47% vs. 26%; p = 0.03). There were no significant differences in follow up time, HPV or p16 status (Table 2).

OTSCC in the young population was significantly more likely to recur, with a hazard ratio of 3.0 (95% Confidence Interval (CI) 1.2–7.3) for 3-year recurrence relative to older patients in a stratified Cox regression model (Fig. 1). The hazard ratio was 3.9 (95% CI 1.4–10.5) after adjusting for alcohol and tobacco use. The most common site for recurrence in young patients was the neck (n = 13) followed by the primary site (n = 9) and the lung (n = 2). The most common site in