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

Table 2
Demographics, behaviors, treatment characteristics, and survival for matched patients.

	Age < 45 *(n = 56)*		Age 45+ *(n = 56)*		P-value
	No.	%	No.	%	
Age category					
< 30 (n = 18)	18	32%			
30–45 (n = 38)	38	68%			
45–60 (n = 26)			26	46%	
60–75 (n = 19)			19	34%	
75+ (n = 11)			11	20%	
Sex					
Male (n = 58)	27	48%	31	55%	0.449
Female (n = 54)	29	52%	25	45%	
Race					
White (n = 108)	54	96%	54	96%	> 0.99
Black (n = 4)	2	4%	2	4%	
Tobacco use					
No tobacco (n = 50)	30	55%	20	36%	0.046
Tobacco use (n = 61)	25	45%	36	64%	
Tobacco type					
Cigarettes (n = 54)	21	38%	33	59%	0.029
Cigars (n = 5)	2	4%	3	5%	0.647
Chewing tobacco (n = 7)	5	9%	2	4%	0.242
Tobacco history					
< 10 years (n = 67)	42	76%	25	45%	0.001
10+ years (n = 43)	13	24%	30	55%	
Total (n = 110)	55	100%	55	100%	
Alcohol use					
Non-drinker (n = 68)	38	69%	30	55%	0.116
Drinker (n = 42)	17	31%	25	45%	
Drinks per day					
< 1 drink/day (n = 81)	44	80%	37	67%	0.13
1+ drink/day (n = 29)	11	20%	18	33%	
T stage					
1 (n = 51)	26	46%	25	45%	> 0.99*
2 (n = 43)	21	38%	22	39%	
3 (n = 16)	8	14%	8	14%	
4 (n = 2)	1	2%	1	2%	
N stage					
0 (n = 78)	39	70%	39	70%	> 0.99**
1 (n = 13)	6	11%	7	12%	
2 (n = 20)	11	20%	9	16%	
3 (n = 1)	0	0%	1	2%	
HPV status					
Negative (n = 37)	18	32%	19	34%	> 0.99
Positive (n = 2)	1	2%	1	2%	
Not tested (n = 73)	37	66%	36	64%	
p16 status					
Negative (n = 33)	17	30%	16	29%	0.916
Positive (n = 9)	5	9%	4	7%	
Not tested (n = 70)	34	61%	36	64%	
Primary treatment type					
Palliative (n = 2)	1	2%	1	2%	0.696***
Radiation or chemoradiation (n = 7)	3	5%	4	7%	
Surgery (n = 101)	51	93%	50	91%	
Adjuvant therapy with surgery					
Surgery Only (n = 64)	27	53%	37	74%	0.028****
Surgery w adjuvant chemoradiation (n = 24)	16	31%	8	16%	
Surgery w adjuvant radiation (n = 12)	7	14%	5	10%	
Surgery w induction chemotherapy (n = 1)	1	2%	0	0%	
Pathological variables					
Positive surgical margins (n = 15)	9	18%	6	12%	0.401
Lymphovascular invasion (n = 14)	9	18%	5	10%	0.142
Perineural invasion (n = 14)	9	18%	5	10%	0.155
Either PNI or LVI (n = 25)	16	36%	9	18%	0.044
Neck dissection					
No (n = 25)	13	28%	12	24%	0.677
Yes (n = 70)	33	72%	37	76%	
Extracapsular spread (n = 11)	6	20%	5	19%	0.637
Occult nodal metastases (n = 4)	3	11%	1	4%	0.38
Median follow up time (months)	43		53		0.93

* P-value for high-stage vs. low stage.
** P-value for N0 vs. N+.
*** P-value for surgery vs. radiation/chemoradiation.
**** P-value for adjuvant therapy vs. no adjuvant therapy.

older patients was the primary site (n = 3) followed by the neck (n = 3) and the lung (n = 2).

Despite the increased recurrence, there was no significant difference in disease-specific or overall survival between young and older patients at 3 years in both adjusted and unadjusted models (HR 2.8; 95% CI 0.3–26.0 for disease-specific mortality among young patients in adjusted model; HR 0.6; 95% CI 0.2–2.2 for overall mortality). The overall survival estimates at 3 years were 86% for younger patients and 84% for older patients; the disease-specific survival estimates were 88% for younger patients and 95% for older patients.

When treating age as a continuous variable, there is a significantly decreased risk of recurrence as age increases, with a hazard ratio of 0.72 (95% CI 0.54–0.96) for each additional 10 years. There was no significant association with overall survival (HR 1.2; 95% CI 0.93–1.74).

Prognostic variables for survival

Prognostic variables for 3-year disease free survival were examined in both younger and older patients. While a high T-stage at presentation was associated with poor disease-free survival in the older patients (HR 13.2; 95% CI 2.0–88.4), there were no associations with disease-free survival in the younger cases (Table 3).

Discussion

In this study, we compared the demographics, behaviors, treatment courses, and disease-free survival of older and younger OTSCC patients at our institution. We found that younger patients were significantly more likely to be female, to abstain from tobacco or alcohol, and to present at a lower T-stage. In a cohort matched on race and stage at presentation, younger OTSCC cases were more likely to recur within 3 years, although there were no significant differences in overall mortality. Younger patients were also significantly more likely to have had either LVI or PNI, and to have received adjuvant therapy in addition to surgery. T-stage was a significant predictor for 3-year disease-free survival in older patients; there were no significant predictors among the variables that we examined in younger patients.

This is the largest matched study examining OTSCC patients in the

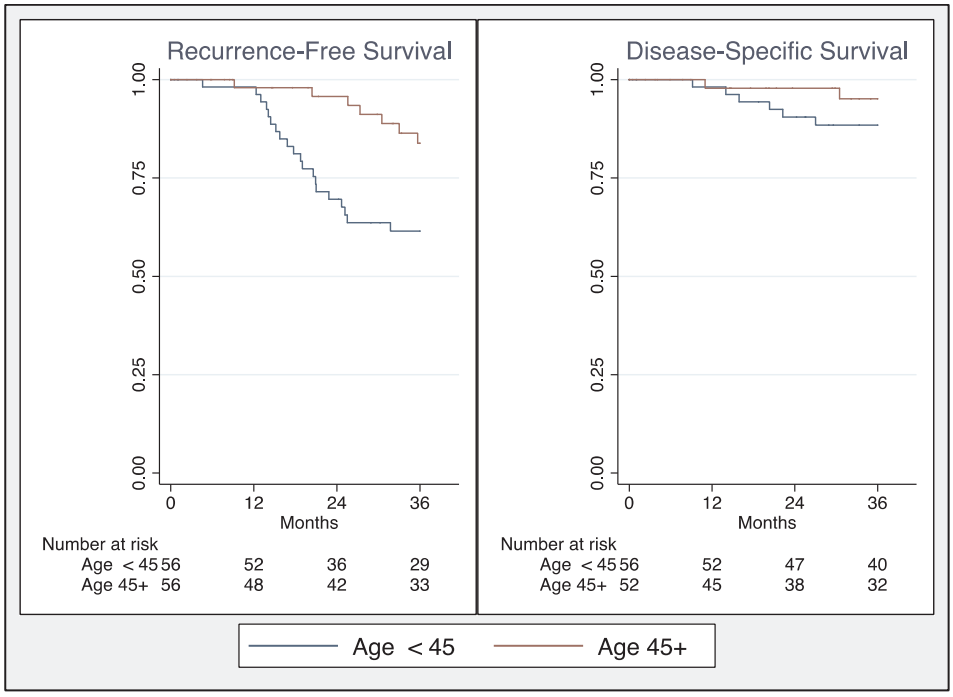

Fig. 1. 3-Year recurrence-free survival and disease-specific survival for matched younger and older patients.

Table 3
Predictors of disease-free survival in matched cohorts.

	Age < 45			Age 45+		
Variables	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex	0.7	0.3–1.8	0.51	0.6	0.1–3.5	0.58
Tobacco history (10+ years)	1.1	0.4–3.2	0.79	1.5	0.2–9.1	0.67
T stage	1.6	0.6–4.8	0.38	13.2	2.0–88.4	0.01
N stage	1.1	0.4–3.1	0.89	2	0.4–11.3	0.42
Alcohol history	0.6	0.2–1.9	0.41	1	1.0–1.0	0.11

United States, and suggests a more aggressive OTSCC phenotype among younger patients. Previous literature on this topic is inconsistent, and most previous studies were unmatched cohort studies [2,16,18,22], or used matching but may have been underpowered [23–27]. In the largest prior US study, Friedman et al. (1998) examined recurrence and survival for 36 OTSCC patients matched under 40 years of age and found a higher rate of locoregional failure and no difference in overall survival compared to older OTSCC patients [28]. Other studies including Pitman et al. (2000) and Siegelmann-Danieli et al. (1998) examined fewer patients (28 and 30 young patients respectively) and found no significant differences in recurrence or survival [23,24].

In contrast, two previous European studies demonstrated worse prognosis and a more aggressive disease among young patients. Garavello et al. (2007) matched 46 Italian OTSCC cases under 40 with 92 older OTSCC controls, and found a significantly worse overall and disease-free survival in the young [29]. While another European study, Blanchard et al. (2017), examining 50 matched French OTSCC cases and controls and found no differences in overall or disease-free survival, almost all failures among young patients occurred within two years of treatment, sooner than the older patients [21].

In addition to differences in disease-free survival, our findings suggest a distinct clinical phenotype associated OTSCC in younger patients. Younger OTSCC patients were more likely to be female, non-smokers, and non-drinkers. These findings are consistent with previous epidemiologic studies in head and neck cancer among non-smokers [11], risk factors for head and neck cancer in multiple cohorts [12] and the changing epidemiology of tongue cancer over time [6,10].

It is notable that matched younger patients were more likely to have LVI or PNI, as well as recurrent cancer. This finding further suggests that tongue cancer among younger patients may represent a more aggressive subtype.

This study has several limitations. Chiefly, it was conducted at a single institution. Another limitation is that older patients may have a higher risk of mortality from other causes; however, the mean age of the older patients in the matched cohort was only 64, and the overall mortality rate was roughly equivalent. A further limitation is that this study used the 7th edition AJCC criteria for staging tongue cancer which did not include depth-of-invasion; the 8th edition staging system may have greater prognostic value [30]. A final limitation was that only a subset of patients received HPV testing. However, HPV occurs in a minority of OTSCC patients [2,4], and HPV-positive OTSCC has not been shown have the same characteristics as HPV-positive oropharyngeal cancers [14].

Overall, the differences in risk factors, pathologic markers, and recurrence rates between older and younger patients seen in this study and others suggest that some OTSCC among younger patients may be distinct from traditional OTSCC. The difference may be analogous to HPV-positive oropharyngeal cancer, which has separate risk factors and a better prognosis than HPV-negative oropharyngeal cancer, as well as distinct genetic and histopathologic characteristics [31–33]. Nonetheless, unlike with oropharyngeal carcinoma, studies examining of OTSCC have yet to find substantial genetic differences between cancers in older and younger patients [34,35], nor any evidence of viral DNA in the tumors of young, non-smoking patients [22].

Additional prospective studies are needed to examine recurrence and survival among young OTSCC patients. If more research demonstrates an increased risk of recurrence, younger OTSCC patients may require additional monitoring or adjuvant therapy. Likewise, further research is warranted into the risk factors for this disease. Large studies involving in-depth interviews or surveys may uncover novel risk factors that are not associated with traditional OTSCC. Finally, more research

is needed into the molecular characteristics of OTSCC in young patients, to determine whether there may be distinct genetic signatures that could account for disparities in prognosis.

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Conflicts of interests

None declared.

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