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Clinical features and outcomes in young adults with oral tongue cancer

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ABSTRACT

Objective: To evaluate outcomes and survival in young patients with oral tongue cancer (OTC).

Methods: Retrospective chart review of patients aged 18–40 with OTC treated between 2000 and 2016. Tumor characteristics of p16 expression, perineural invasion (PNI), and lymph-vascular invasion (LVI) were evaluated. Recurrence-free (RFS) and overall survival (OS) data were analyzed according to Kaplan-Meier method with univariate analysis.

Results: A total of 23 patients were identified: 12 with early stage disease (ESD, stage I), and 11 with advanced stage disease (ASD, stage III or IV), (17 men and 6 women). Mean age at presentation was 34.5 years (± 5 months) and mean follow-up was 46.6 months. For all patients, 5-year RFS was 62% and OS 66%. RFS for ESD was 73% and ASD 25% (log rank p = 0.011). OS for ESD was 100% and ASD 55% (log rank p = 0.012). 22% indicated tobacco use > 5 pack-years and 9% heavy alcohol use. Factors associated with worse OS were neck disease (log rank p = 0.073), positive margins (log rank p = 0.001), and LVI (log rank p = 0.002). Factors associated with worse RFS were chemotherapy or radiation therapy prior to surgery (log rank p = 0.002), neck disease (log rank p = 0.047), positive margins (log rank p = 0.039), and PNI (log rank p = 0.001). Expression of p16 was observed in five cases and was not significantly associated with OS or RFS.

Conclusion: In young patients with OTC, factors associated with worse outcomes are similar to known predictors in older patients. Expression of p16 was not statistically associated with improved OS. OS in patients with ESD was excellent (100%), and significantly worse for ASD.

1. Introduction

In the U.S., head and neck squamous cell cancers (HNSCC) accounts for 3% of malignancies, with approximately 63,000 diagnoses and 13,000 deaths annually [1]. Oral-cavity squamous-cell carcinoma is the eighth most common cancer worldwide [1]. In the U.S., OCSCC contributes to 2% to 4% of new malignancies yearly, with around 8000 deaths/year [1]. The most common site of oral cancer is the anterior two thirds of the tongue, representing 22% to 49% of all oral cancers diagnosed [1].

There are two classic groups of HNSCC patients. There first group consists of older patients, in their sixth to seventh decade of life, usually male, with significant alcohol and/or tobacco exposure [2,3]. The second group includes those younger, in their fourth to fifth decade of life, with human papillomavirus (HPV) associated tumors in the oropharynx and p16 over-expression [2–4]. These patients are likely to be never-smokers/never-drinkers [2–4]. A unique subgroup of patients in this nonsmoker group has been identified that includes very young patients, often < 45 years old, with squamous cell cancers of the oral tongue [2–5].

The incidence of oral tongue cancer (OTC) in this population is increasing according to recent reports. An analysis conducted on combined tumor registry data from Denmark, Sweden, Norway, and Finland showed that between 1960 and 1994, 5.5% of tongue cancers occurred in patients aged 20 to 39 years [6]. During this time period, the incidence of oral cancer increased 5-fold among young men and 6-fold among young women, compared with only a 2-fold increase in the older age group [6]. Additionally, investigators in the U.S. and Europe report increasing incidence rates of tongue SCC among people < 45 years of age [7]. Shiboski et al. found a significant increase in the incidence of oral tongue SCC and SCC of the base of the tongue among younger white individuals, using the Surveillance, Epidemiology, and End Results Data base for 1973 to 2001 in the US population aged 20 to 44 years [7].

Although the increase in incidence among tumors of the oropharynx, particularly tonsillar and tongue base cancer, are shown to be related to HPV, the literature suggests HPV is unlikely to play an important role in in the rising trend of OTC, particularly in the very

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young patients [2–5]. Over-expression of p16 does not seem to be not an appropriate biomarker for HPV-association in OTC as it is in oropharyngeal cancers (OPC) [3–5]. There are inconsistent reports on the significance of p16 expression in young adults with OTC. Some authors suggest that p16 over-expression is common and a marker of favorable prognosis [2,8], while others note p16 expression to be a significant predictor of poorer outcome with increased risk of death and recurrence [5].

Because of the limited data and disparity of results reported thus far in the literature on this age group, we performed a retrospective chart review examining patients between the ages of 18–40 who were diagnosed with OTC at a single institution. The aim was to determine the clinicopathologic factors, including p16 status, the management, and the recurrence-free survival and overall survival among young patients with OTC.

2. Materials and methods

This is a retrospective chart review of all patients between 18 and 40 years of age with squamous cell carcinoma of the oral tongue treated at Rush University Medical Center (RUMC) between 2000 and 2016. The study was approved by the institutional review board.

Patient demographic and clinical characteristics were collected including age, sex, tobacco and alcohol status, cancer treatment, most recent follow-up, and current medical status. For patients with unknown medical status, the Social Security Death Index was used to confirm if that patient was currently still alive or deceased as of 2014. Tumor characteristics were collected including location, stage, grade, p16 status, recurrence status, margin status, depth of invasion, perineural invasion, and lymphovascular invasion.

Beginning in 2000, RUMC pathology department began to routinely stain HNSCC tumor samples for p16-expression. Formalin- fixed paraffin-embedded specimens were assessed for p16 by using standard immunohistochemistry method. p16 was considered positive when a diffuse and strong immunoreaction of p16 was noted in the cytoplasm and nucleus of > 70% of the tumor cells.

Recurrence-free survival (RFS) and overall survival (OS) data were analyzed according to Kaplan-Meier method with univariate analysis. Duration of follow-up was calculated from the date of definitive treatment (surgery) to the date of the outcome of interest (e.g., recurrence or death); otherwise, the duration of follow-up was censored at the date of last follow-up. All calculated p-values were 2 sided, and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

A total of 23 patients between the ages of 18–40 diagnosed with oral tongue cancer were included in this study. Seventeen men (74%) and 6 women (26%) with a median age of patients was 36 years (range, 22–40 years). Mean age at diagnosis was 34.5 years (± 5 months). Five patients (22%) had significant tobacco abuse as defined as five pack years or more. Two patients (9%) had significant alcohol use (defined as daily use). One patient had significant alcohol use in addition to tobacco use. The distribution of primary sites on the oral tongue were right lateral (61%), left lateral (35%) and anterior midline (4%). The mean (SD) follow-up duration was 46.6 (54.6) months. The median follow-up was 26 months. The range was 1 to 215 months. Relevant patient clinicopathological data are given in Table 1.

3.2. Tumor characteristics and staging

Ten patients had a histopathologic grade I tumor (well-differentiated SCC), 11 grade II (moderately-differentiated), and 2 grade III tumors (poorly-differentiated). Average depth of invasion (SD) was 5.6 mm (5.1 mm), median 4 mm, with a range of 0.6–19 mm. Four cases had evidence of perineurial invasion. Two had evidence of lymphovascular invasion. One had positive margins.

Table 1
Clinicopathological data.

Variables	Total (n = 23)	p16-positive (n = 5)	p16-negative (n = 15)	Unknown (n = 3)
Age at diagnosis (years), median	36	37	34	39
Male	17	4	10	3
Female	6	1	5	0
Smoking history	5	1	3	1
Alcohol history	2	0	2	0
T stage				
T1	19	3	13	3
T2	3	1	2	0
T3	1	1	0	0
N stage				
N0	12	1	9	2
N1	9	3	5	1
N2	2	1	1	0
AJCC stage				
I	12	1	9	2
II	0	0	0	0
III	9	3	5	1
IV	2	1	1	0
Histopathological grade				
Grade 1	10	2	5	3
Grade 2	11	1	10	0
Grade 3	2	2	0	0
Depth of invasion, median (mm)	4	4	4.5	2
< 5	13	3	7	3
5–10	6	0	6	0
> 10	3	2	1	0
Margins				
Positive	1	0	1	–
Negative	21	5	14	2
Lymphovascular invasion	2	0	2	0
Perineural invasion	4	1	3	0
Initial treatment				
Surgery alone	13	1	11	1
CRT alone	2	1	1	0
Surgery + CRT	8	3	3	2
Recurrence (%)	11 (48%)	2 (40%)	7 (46.7%)	2 (66.7%)
Deceased (%)	6 (26%)	0 (0%)	5 (33.3%)	1 (33.3%)

All patients were staged with combination of clinical examination and imaging according to 7th American Joint Committee on Cancer (AJCC) staging system. Twelve cases had early stage disease (ESD) at diagnosis: 12 stage I, 0 stage II. Eleven had advanced stage disease (ASD) at diagnosis: 9 stage III and 2 stage IVa. Eleven patients (48%) had evidence of neck disease clinically.

Twenty-one patients had a sufficient primary tumor sample for p16 testing and detection. Five samples (23.8%) were p16-positive. Of these 5 patients, 1 had ESD at diagnosis and 4 had ASD.

3.3. Treatment

Twenty-one patients underwent surgery as first-line definitive treatment. Two patients underwent systemic treatment first followed by surgery after recurrence occurred. Overall, 9 patients received adjuvant treatment with 6 receiving post-operative chemoradiation therapy and 3 receiving post-operative radiation therapy alone. A total of fifteen patients underwent neck dissection throughout the study period.

3.4. Recurrence

Five-year RFS was 61%. Median time to recurrence was 10 months,

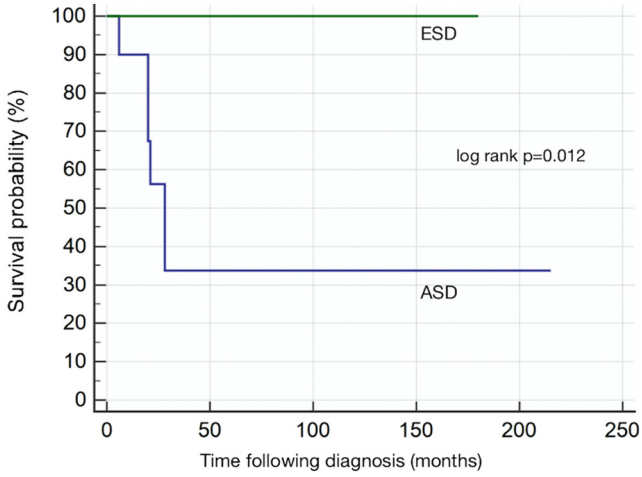

Fig. 1. Overall survival by stage of disease at diagnosis.

with a range of 4–156 months. A total of eleven patients developed recurrence throughout the study period: 6 local, 2 regional, 1 distant and 2 with both local and regional recurrence. Eight patients with recurrence had further surgery and/or adjuvant CRT therapy. Four among the 11 patients developed subsequent recurrence. Six patients (55%) were deceased at the time of this study preparation.

RFS for patients with ESD and ASD was 73% and 25% respectively (log rank p = 0.011). Additional factors significantly associated with worse RFS as identified by univariate analysis were nodal involvement (log rank p = 0.011), chemotherapy or radiation therapy prior to definitive surgery (log rank p = 0.002), positive surgical margins (log rank p = 0.039) and perineurial invasion (log rank p = 0.0001).

3.5. Survival

Six deaths were reported among the 23 patients. Five-year OS was 67% for all patients. Median time to death was 20.5 months with a range of 6–28 months. Factors associated with significantly worse OS were ASD at diagnosis (log rank p = 0.012) (Fig. 1), nodal involvement (log rank p = 0.012), positive surgical margins (log rank p = 0.0001), and lymphovascular invasion (log rank p = 0.002). Seventeen patients were alive at last follow-up of which 16 had no evidence of disease. Smoking and alcohol were not found to be significantly associated with RFS or OS.

3.6. p16 status

Expression of p16 was observed in 5 of 21 samples tested (23.8%) and was not significantly associated with RFS (log rank p = 0.751) or OS (log rank p = 0.205) (Fig. 2). Two of the p16-positive cases had local or regional recurrence, however all were alive with no evidence of disease at most recent follow up.

A summary of the factors evaluated for an association with RFS and OS is presented in Table 2.

4. Discussion

Although oral tongue squamous cell carcinoma is a rare disease, contributing to 2% to 4% of new malignancies each year in the US, its incidence is increasing, especially in young adults [1,6,7]. There are inconsistent reports in the literature regarding the significance of p16 positivity in young adults with oral tongue cancer. Therefore we conducted a retrospective analysis of all patients 40 years and younger treated at our institution from 2000 to present for OTC looking at management and outcomes in this population. Our institution began routinely staining for p16 in head and neck tumor samples in 2000. This

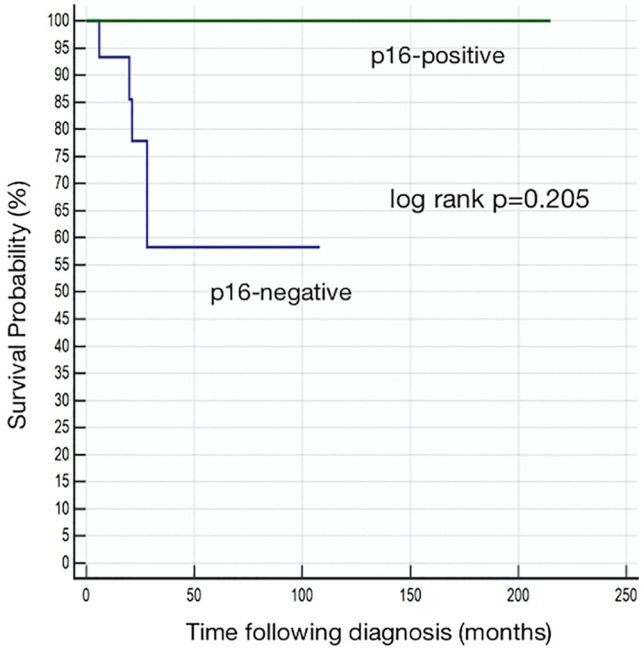

Fig. 2. Overall survival by p16 expression status.

Table 2
Univariate analysis.

Variable	Recurrence-free Survival log rank p-value	Overall Survival log rank p-value
Male Sex (vs female)	0.124	0.355
Tobacco use	0.898	0.396
Alcohol use	0.737	0.361
Overall stage, ASD vs ESD	0.011	0.012
N Stage	0.011	0.012
Histopathological grade	0.725	0.976
p16-positive	0.762	0.205
Neck disease	0.047	0.073
Margin status	0.039	0.0001
Perineural invasion	0.0001	0.059
Lymphovascular invasion	0.404	0.002
Adjuvant CRT	0.502	0.194
Primary treatment CRT	0.002	0.773

is not routine at many institutions, hence there was specific interest in how p16-positivity related to recurrence-free and overall survival given the disparity of results and small number of papers on the subject reported thus far in the literature.

In our cohort of 23 patients with OTC, the 5-year RFS was 61% and OS was 67%. The 5-year RFS for patients with stage 1 disease was 73%. This is nearly identical to the 5-year RFS reported in a retrospective study by Thomas et al., which looked at outcomes in oral squamous cell carcinoma in young adults between the ages 18–40 (n = 62) [9]. The reported 5-year RFS was 73.5% for the whole cohort including both ESD and ASD patients [9]. The cohort of 62 patients in the Thomas study had a higher proportion of ESD at diagnosis when compared to our cohort (69.4% vs 52%), hence why the reported 5-year RFS was better than our reported 5-year RFS for our whole cohort but similar to that for patients with stage 1 disease. Similarly, smoking and alcohol intake were not seen as risk factors in this population [9]. Only nodal involvement was associated with significantly worse OS and only extracapsular spread was associated with significantly worse locoregional recurrence [9]. This study looked at epidermal growth factor receptor (EGFR) expression as it relates to prognosis in this population but found no difference in cause-specific survival at 5 years in people with high vs low EGFR expression (HR 3.1, p = 0.46) and this study did not examine

p16 status.

There are few papers that look at the significance of p16 expression in very young adults with OTC. A study by Harris et al. looked specifically at the correlation between p16 expression and prognosis in young patients with OTC. They identified 25 patients between the ages 20–39 and found p16-positivity in 11 of 25 patients (44%), which is just about double the proportion of our sample (23.8%). In this study, p16-positivity correlated with improved relapse-free survival ($p = 0.01$) and OS ($p = 0.05$) [2]. A study by Ramshankar et al. looked at p16 expression in patients with OTC, not specifically in young adults. They found tumors showing p16 over-expression had increased hazard of death (HR = 2.395; $p = 0.005$) and disease recurrence (HR = 2.581; $p = 0.002$) [5]. Fifteen percent of their sample tested positive for p16-expression. Satgunaseelan et al. also looked at p16 expression as it relates to prognosis in patients of all ages with OTC and noted longer disease-specific survival on univariate analysis ($p = 0.044$), and p16 expression present in early stage disease; however, p16 was not an independent predictor of survival [8].

In our cohort, the p16-positive subset of patients (n = 5, 23.8%) had recurrence-free survival of 60% and overall-survival of 100%. Although, these numbers are quite good, p16 was not significantly associated with recurrence-free survival (log rank $p = 0.751$) or overall-survival (log rank 0.205) in any way. This could be due to the low n and power of this group. Our data does not show definitive proof that p16-expression is associated with better or worse prognosis in young adults with OTC.

Our data does provide good insight into management and prognosis in this unique population however. We found that patients who underwent chemoradiation therapy as first-line treatment had significantly higher risk of recurrence than patients who underwent resection primarily (log rank $p = 0.002$). Survival outcomes were shown to be significantly worse in young adults with advanced stage disease, neck disease, positive surgical margins, perineurial invasion, and lymphovascular invasion. Studies comparing different age groups of adults with OTC show these factors are similar to known predictors of worse outcomes in older adults with OTC [10–12].

Zhang et al. noted no difference between patients aged 30 years and 70 years in regards to disease-free survival and disease-specific survival [10]. Among all age groups, advanced stage disease and alcohol/tobacco use were the only factors that significantly influenced DSS [10]. Another study that performed a case-matched analysis did not find a difference among patients with OTC younger or older than 40 years with regard to overall, cancer-specific, or progression-free survival [11]. The only prognostic factor was the performance of surgery, which was associated with significantly improved survival (HR 0.17; 95% CI 0.06, 0.51; $p = 0.001$), as was the case for our cohort [11].

A comparison by age group revealed no differences in histologic grade, rates of advanced T-stage, perineural invasion, vascular invasion, or nodal extracapsular extension among those < 30 years old, 31–60 years old, and > 60 years old [12]. There was no significant difference between RFS and OS among the different age groups. RFS and OS ranged from 50 to 60% and 60–80% respectively, which is comparable to our cohort. All younger patients with recurrent disease died within 16 months compared to 45% of those with recurrence in our cohort.

We acknowledge the main limitations of our study include the retrospective nature of the study, the small cohort size and specific patient population in which we cannot apply our results to larger groups or older patients with OTC. Given that this is a relatively rare condition, this information is helpful in guiding future studies.

5. Conclusion

In young patients (< 40 years old) with oral tongue cancer, factors associated with worse outcomes are similar to known predictors in older patients. Expression of p16 was present in this cohort, however this was not statistically associated with improved OS. Survival outcomes are quite good in young patients with stage 1 disease at diagnosis and significantly worse in young adults diagnosed with ASD. More work needs to be done to understand the etiology of OTC in young adults including genetic analysis.

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Declarations of interest

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References

[1] Müller S. Update from the 4th edition of the World Health Organization of head and neck tumours: tumours of the oral cavity and mobile tongue. Head Neck Pathol 2017;11:33–40.
[2] Harris SL, Thorne LB, Seaman WT, et al. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. Head Neck-J Sci Spec 2011;33:1622–7.
[3] Kabeya M, Furuta R, Kazuyoshi K, et al. Prevalence of human papillomavirus in mobile tongue cancer with particular reference to young patients. Cancer Sci 2012;103:161–8.
[4] Liang XH, Lewis J, Foote R, et al. Prevalence and significance of human papillomavirus in oral tongue cancer: the Mayo Clinic experience. J Oral Maxillofac Surg 2008;66:1875–80.
[5] Ramshankar V, Soundara VT, Shyamsundar V, et al. Risk stratification of early stage oral tongue cancers based on HPV status and p16 immunoexpression. Asian Pac J Cancer Prev 2014;15:8351–9.
[6] Garnaes E, Kiss K, Andersen L, et al. Increasing incidence of base of tongue cancers from 2000 to 2010 due to HPV: the largest demographic study of 210 Danish patients. Br J Cancer 2015;113:131–4.
[7] Shiboski CH, Schmidt BL, Jordan RCK. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer 2005;103:1843–9.
[8] Satgunaseelan L, Virk SA, Lum T, et al. p16 expression independent of human papillomavirus is associated with lower stage and longer disease-free survival in oral cavity squamous cell carcinoma. Pathology 2016;48:441–8.
[9] Thomas L, Moore EJ, McGree ME, et al. Prognostic features, human papillomavirus status, and epidermal growth factor receptor expression in oral squamous cell carcinoma in young adults. Am J Otolaryngol 2012;33:650–6.
[10] Zhang YY, Wang DC, Su JZ, et al. Clinicopathological characteristics and outcomes of squamous cell carcinoma of the tongue in different age groups. Head Neck 2017;39:2276–82.
[11] Blanchard P, Belkhir F, Temam S, et al. Outcomes and prognostic factors for squamous cell carcinoma of the oral tongue in young adults: a single-institution case-matched analysis. Eur Arch Otorhinolaryngol 2017;274:1683–90.
[12] Hilly O, Shkedy Y, Hod R, et al. Carcinoma of the oral tongue in patients younger than 30 years: comparison with patients older than 60 years. Oral Oncol 2013;49:987–90.