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# Early onset oral tongue squamous cell carcinoma: associated factors and patient outcomes

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## Abstract

**Background:** Incidence of oral tongue squamous cell carcinoma (OTC) is rising among those under age 50. The etiology is unknown.

**Methods:** 395 cases of OTC diagnosed and/or treated at Vanderbilt University Medical Center between 2000 and 2017 were identified. 113 (28.6%) were early onset (< age 50). Logistic regression was used to identify factors associated with early onset OTC. Cox proportional hazards models evaluated survival and recurrence.

**Results:** Compared to typical onset patients, early onset OTC patients were more likely to receive multimodality treatment (surgery & radiation; adjusted odds ratio [aOR]:2.7, 95%CI:1.2–6.3) and report a history of snuff use (aOR:5.4,95% CI:1.8–15.8) and were less likely to report a history of cigarette use (aOR:0.5, 95%CI:0.2–0.9). Early onset patients had better overall survival (adjusted hazard ratio [aHR]: 0.6).

**Conclusions:** This is the largest study to evaluate factors associated with early onset OTC and the first to report an association with snuff.

### Keywords

oral tongue; squamous cell carcinoma; young; tobacco; snuff

## INTRODUCTION

Tobacco use in the US has been declining over the last few decades, and with it, the incidence of many head and neck cancers[1,2]. However, the incidence of two head and neck cancer subtypes, oropharyngeal squamous cell carcinoma (OPC) and oral tongue squamous cell carcinoma (OTC), are rising[3]. The increase in OTC incidence is primarily occurring

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within young (<50 years of age) white males and females[3]. The rise in incidence of OPC has been attributed to human papillomavirus infection; yet, for OTC, no single cause has been identified[4].

Despite the rapid increase in incidence of early onset OTC in the US, few studies have been performed to evaluate risk factors, prognosis, and survival[5–12]. Previous studies were small (range: 6–79 early onset patients), lacked detailed information on traditional head and neck cancer risk factors, and reported mixed findings. Early reports suggested that early onset OTC was not associated with classical head and neck cancer risk factors such as alcohol and tobacco use and was associated with worse prognosis than typical onset OTC[13,14]. Yet, several recent studies identified alcohol and tobacco use as the main risk factors for early onset OTC and found no difference in survival between early and typical onset OTC, including in a systematic review of 11 OTC studies by de Morais[15–17]. Given the limitations of prior studies and the increasing incidence of OTC, larger studies with more detailed clinical information on patient prognosis as well as the traditional head and neck cancer risk factors are needed.

The objective of this study was to compare the distribution of traditional head and neck cancer risk factors and patient prognosis between early (< age 50) and typical onset (age 50 or greater) OTC within a large cohort of patients. We compiled a large retrospective clinical cohort of 395 OTC patients diagnosed and/or treated at Vanderbilt University Medical Center (VUMC) between January 1, 2000 and January 16, 2017 with detailed environmental risk factor information (tobacco [cigarettes, pipe, cigars, snuff, chew; amount and duration of use] and alcohol use) and patient outcome data. To our knowledge, this is the largest US-based study to assess risk factors and prognosis associated with early onset OTC.

## MATERIALS AND METHODS

### Study Population

Incident, previously untreated cases of OTC were identified though the Vanderbilt Research Derivative (RD), an IRB-approved, identified, searchable database of more than 3.5 million electronic health records (EHRs) from patients seen at VUMC[18]. The RD contains clinical data collected as part of routine patient care but reorganized to be easily searchable and usable for research purposes. The RD also links with the Vanderbilt Cancer Registry (VCR), which collects detailed clinical information from all reportable neoplasms diagnosed and/or treated at VUMC.

Patients diagnosed with OTC between January 1, 2000 and January 16, 2017 were identified using the following International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes: C02.0, C02.1, C02.2, C02.3, C02.8, C02.9. This date range was chosen because the year 2000 was the earliest year in which clinical data was reliably captured in EHRs at VUMC. A complete manual review of each patient's EHR was conducted to: a) determine whether the patient had a prior history of cancer (other than non-melanoma skin cancer) and b) confirm the OTC diagnosis. Only confirmed incident cases of OTC without a prior history of cancer (other than non-melanoma skin cancer) were included in this study (N=395). Of the 567 OTC patients identified, 17 (3.0%) were excluded due to a prior cancer, 44 (7.8%)

were excluded due to misclassification as OTC, and 11 (1.9%) were excluded due to a lack of sufficient records to confirm eligibility (Supplemental Fig. 1).

## Clinical Data Abstraction

For the confirmed incident cases of OTC, an additional manual review of the EHR was conducted to obtain variables such as tobacco exposure (cigarette, cigar, pipe, snuff, and chew; amount and duration of use), alcohol exposure (amount and duration of use), treatment course, treatment responses, outcome, and last known follow up. Demographic and tumor characteristics were obtained from the RD (Supplemental Table 1). Pathologic and molecular characteristics of the tumors, such as HPV testing, were beyond the scope of this analysis. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt University[19].

## Statistical Analyses

Patient characteristics were evaluated overall and by age of onset of OTC (early [<age 50] or typical [age 50+). These cutoffs were chosen based on a recent study of SEER data that demonstrated that OTC incidence was increasing nationally among those less than age 50[3]. Determinants for early onset OTC were first evaluated in univariate models. To evaluate the independent determinants of early onset OTC, factors significantly associated with early onset OTC in the univariate analysis or considered important based on the literature (i.e., gender, race, clinical stage), were included in the multivariate model as covariates to estimate an adjusted odds ratio (aOR). Additional sensitivity analyses were performed by modifying the age definition of early onset OTC.

Alcohol use was categorized separately by gender according to CDC guidelines[20]: no alcohol use (<12 drinks in lifetime); light use (12+ drinks in lifetime, but <1 drink/week); mild to moderate use (1–7 drinks/week [females], 1–14 drinks/week [males]); heavy use (8+ alcoholic drinks/week [females], 15+ drinks/week [males]). Tobacco use was determined at the time of diagnosis. One product-year was defined as one pack of cigarettes, one cigar, one pipe, one can of snuff, or one pouch of chewing tobacco per day per year.

The association between onset of OTC (early vs. typical) and a) overall survival; and b) time to recurrence (local, regional, and distant combined) were evaluated by estimating hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards models; years since cancer diagnosis was used as the time variable. To assess risk of death from any cause, the only censoring event was at time of last known follow-up. For overall recurrence, the analysis was restricted to those who had a complete response at the end of treatment, which was determined at the patient's 3-month post-treatment oncologic visit and was defined as no clinical and/or radiographic evidence of disease. Follow up ended at time of first recurrence (local, regional, or distant) with censoring events consisting of death or last oncologic follow-up. To account for differences in baseline patient characteristics and treatment, Cox proportional hazards models for survival and recurrence were adjusted for sex, race, overall clinical stage, treatment, alcohol use at diagnosis, and ever vs. never tobacco use. Survival and recurrence analyses were also stratified by never versus ever tobacco use status.

A predictive model for overall survival was generated using recursive partitioning. The resulting model was then pruned to the size resulting in optimal cross validation error. Observations with missing values or whose tumor classification was classified as TX were classified using surrogate variables. Analyses were performed by STATA IC version 15 and R version 3.3.2. P-values less than 0.05 (2-tailed) were considered statistically significant.

## RESULTS

### Patient Characteristics

Among the 395 patients with incident OTC, median age was 58 (interquartile range [IQR]: 48–67). The majority of patients were white (95.2%), male (60.2%), stage I-II (59.5%; AJCC 6$^{th}$ and 7$^{th}$ Editions), treated with surgical resection alone (58.2%), never or light alcohol users (50.6%), and current or past tobacco users (64.0%) (Supplemental Table 2).

### Risk Factors Analysis

Compared to typical onset OTC, early onset patients were significantly less likely to report a history of cigarette smoking and heavy alcohol use at the time of diagnosis. Early onset OTC patients were also significantly more likely to receive surgical resection plus radiation therapy, and to be never tobacco users. Yet, early onset patients were significantly more likely to report snuff use (Table 1). Forty-six percent of early onset OTC patients were never tobacco users (Table 1). More importantly, 37% of early onset OTC patients had no history of traditional head and neck cancer risk factors (tobacco use and/or heavy alcohol use). In the multivariate analysis, snuff use (aOR: 5.4, 95% CI: 1.8–15.8), multimodality treatment (aOR: 2.7, 95% CI: 1.2–6.3 [surgery plus radiation]), and former cigarette smoking (aOR: 0.5, 95% CI: 0.2–0.9) remained significant (Table 1). In sensitivity analyses, the association between snuff use and early onset OTC strengthened as the age cutoff for defining early onset OTC was decreased (Supplemental Table 3).

### Cumulative Survival All-Cause Mortality

Median follow-up for our study was 27.2 months (IQR:11.9–64.2 months). Five and 10-year survival rates for early onset OTC were 75.8% and 64.1%, respectively compared to 71.0% and 46.7% for typical onset OTC (Fig. 1). Compared to typical onset, early onset OTC was associated with an almost 50 percent reduction in hazard of death (adjusted hazard ratio [aHR]:0.6, 95% CI: 0.3–0.9) (Table 2). In analyses stratified by tobacco use, the association of early onset OTC with improved survival was strongest among patients who were tobacco users (aHR:0.3, 95% CI:0.1–0.8) (Supplemental Table 4).

### Risk of Recurrence

Three hundred and sixty-two (92%) of the 395 patients were assessed for recurrence; 33 patients either had residual disease following treatment completion or were lost to follow-up. One hundred and thirty-six 136 (37.6%) patients recurred (75 local; 66 regional; 13 distant). Two and 5-year recurrence rates for early versus typical onset OTC were 35.2% and 45.5%, and 32.5% and 44.3%, respectively (Fig. 1). No association between age of OTC onset and risk of recurrence was observed (Table 2). Additionally, no associations were observed in analyses stratified by tobacco use (Supplemental Table 4).

### Recursive Partitioning Analysis

Using recursive partitioning analysis, patient age at OTC diagnosis (≤ age 65 vs. > age 65) and N classification (N0 vs. N1+) were identified as the major factors influencing survival. Tobacco use was not identified as a predictor for risk of death. Patients were classified into three groups with respect to risk of death from all causes (Fig. 2). The group with the lowest risk of death (HR: 0.6) was patients aged 65 or less without nodal disease. The group with the highest risk of death (HR: 1.6) was patients older than 65. Interestingly, risk of death for those less than age 65 varied greatly based on the presence of nodal metastases (HR: 0.6 for N0 and 1.4 for N1+).

## DISCUSSION

This is the largest study to date to evaluate risk factors associated with early onset OTC and the first study to report an association between early onset OTC and snuff use – a type of smokeless tobacco that is becoming increasingly popular with younger birth cohorts[21]. Use of other smokeless tobacco products such as chewing tobacco have also been on the rise[22]. However, no associations between early onset OTC and chewing tobacco use nor with any other tobacco products (cigarette, cigar, or pipe) were observed. Early onset OTC was also associated with improved overall survival, particularly among ever tobacco users. No significant difference in recurrence was observed. In the recursive partitioning analysis, patient age at diagnosis and N classification were the main factors influencing survival.

Despite the increasing incidence of OTC among younger birth cohorts in the US, few studies have evaluated risk factors associated with early onset OTC. Of the few studies conducted to date, results have been conflicting. A study by Friedlander et al. showed no significant difference in alcohol use between younger and older patients with OTC[8], while a study by Siegelmann-Danieli et al. found that there was significantly less heavy alcohol and tobacco (cigarette, cigar, and chewing tobacco) use in early versus typical onset OTC patients[9]. Although snuff was first hypothesized to be a cause of increased incidence and mortality of early onset OTC in the 1980s[23,24], our study is the first to report an association. Previous studies have not been powered to detect an association and/or limited their analyses to patients with tobacco use or cigarette smoking history. Only three prior studies have explicitly included non-cigarette tobacco products, such as cigars and chewing tobacco, in their analyses[5,7,9]. Schantz et al. and Sarkaria & Harari found that over half of patients with early onset OTC either smoked cigarettes or used chewing tobacco, but they did not perform separate analyses for each tobacco product[5,7]. While, Siegelmann-Danieli et al. observed significantly less combined cigarette, cigar, chewing tobacco, and heavy alcohol use in early onset OTC patients than in patients with typical onset OTC[9].

Reports of survival among early versus late onset OTC have also been conflicting. The first reports of early onset OTC in the US indicated a worse overall patient prognosis with increased mortality[13,14,25]. Yet, more recent studies, such as our own, suggest that early onset OTC is associated with better overall survival than typical onset OTC[11,12]. The discrepancy between earlier and more recent reports could be due to better recognition of the changing epidemiologic trends in this disease resulting in better recognition of OTC in younger patients. Additionally, the earlier reports of poorer prognosis among early onset

patients may have influenced how younger patients were subsequently treated. We did find that early onset patients received more aggressive treatment than their typical onset counterparts, despite no difference in overall clinical staging. Contrary to our observation, current guidelines issued by the National Comprehensive Cancer Network do not specify a change in treatment approach based on age[26]; yet, our findings suggest that age-stratified treatment approaches should potentially be evaluated in the future. Additionally, while some studies have reported higher locoregional recurrence rates in patients with early onset OTC[8,10], we did not observe a significant difference in recurrence rates among those with early versus typical onset OTC. Results of the recursive partitioning analysis showed age of diagnosis and N classification were the strongest predictors of prognosis. Older patients (> age 65) had the worst overall survival, while younger patients (≤ age 65) with N0 classification had the best prognosis.

Our study has several strengths. With a cohort size of 395 OTC patients, 113 of which were early onset, this study is the largest study conducted in the United States to evaluate risk factors and prognosis among patients with early onset OTC. We had access to detailed alcohol and tobacco use information (product, amount and duration of use), through the Vanderbilt Head and Neck Clinic Patient Intake form which was routinely given to all cancer patients from mid-2003 onward. We also had high quality clinical data on the patients included in this study due to VUMC being an early adopter of electronic health records.

Our study also had several limitations. We did not include patients without OTC in our analyses; thus, the lack of an unaffected control group limited our ability to delineate whether the factors associated with early onset OTC were specific to OTC patients or were solely due to differences in patient age. However, the proportion of snuff use in our early onset OTC patients (12.4%) is greater than the reported national snuff use rates for similar age groups (5–6%), suggesting that snuff use may have some causal role in the development of early onset OTC, yet we would expect that snuff use rates are higher than the national average among young people in the “tobacco belt”[27]. This study was conducted retrospectively and relied on patient-reported risk factor data. Therefore, the data may be affected by underreporting due to patient-perceived guilt over engaging in cancer-associated behaviors or over reporting due to recall bias. Nevertheless, both early and typical onset groups should be affected equally, limiting the impact of these potential biases on our analyses.

One limitation of our survival models was that we did not address confounders such as baseline functional status and underlying comorbidities, which could be a cause of the worse survival seen in older patients. Due to the constraints of the EHR system, we were unable to determine disease-specific mortality. Disease-specific survival would allow for better assessment of the observed differences in 10-year survival rates, which may be better in younger people simply because of their age. The similarities in 5-year survival rates (76 vs. 71% for early and typical onset, respectively) may indicate that these two disease entities have similar prognoses. In fact, a study using SEER data found no difference in disease-specific mortality between early and typical onset OTC patients[28]. Another possible reason for better survival in early onset patients is that some of the cancers may be caused by HPV due to the inclusion of overlapping and unspecified tongue cancers (C02.8 and C02.9).

However, we carefully reviewed each case to confirm the anatomic site of the cancer and excluded all cases with possible overlap with anatomic sites within the oropharynx (Supplemental Fig. 1). Our study was limited to a single tertiary care center, albeit one with a large catchment area in the middle of the "tobacco belt." Finally, we relied on patient records to determine vital status, which may have resulted in an under reporting of mortality outcomes.

Our results suggest that a portion of early onset OTC may be a result of smokeless tobacco product use, particularly snuff. However, only a small proportion of patients with early onset OTC were snuff users (12%), suggesting the presence of additional, unknown risk factors contributing to the rise of early onset OTC among younger individuals. Future work is needed to more comprehensively evaluate early onset OTC risk factors with prospective studies able to obtain more detailed information on potential risk factors prior to cancer diagnosis. Additionally, given the parallels between OPC and OTC in younger patients, larger molecular studies of OTC tumors are needed to evaluate the possibility of an infectious etiology.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements:

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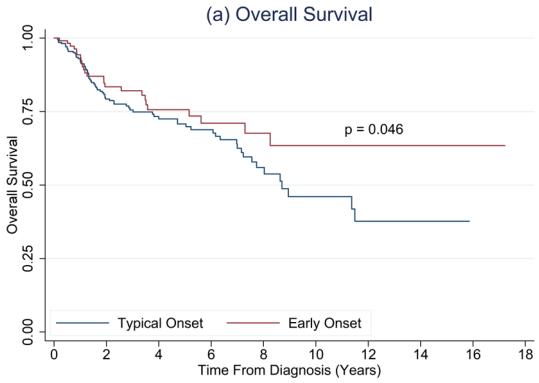
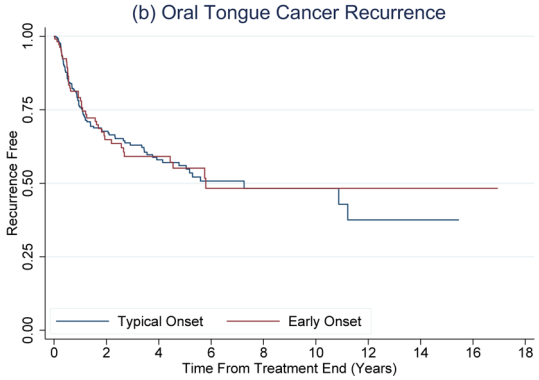



| | Years | | | | | |
|---|---|---|---|---|---|---|
| ***Number at Risk*** | **0** | **2** | **4** | **6** | **8** | **10** |
| **Early Onset** | 113 | 67 | 46 | 29 | 19 | 9 |
| **Typical Onset** | 282 | 149 | 91 | 61 | 27 | 13 |




| | Years | | | | | |
|---|---|---|---|---|---|---|
| ***Number at Risk*** | **0** | **2** | **4** | **6** | **8** | **10** |
| **Early Onset** | 107 | 51 | 31 | 13 | 8 | 5 |
| **Typical Onset** | 255 | 115 | 64 | 33 | 14 | 11 |

**Fig. 1.**

Overall survival and recurrence for typical onset (blue) and early onset (red) OTC. Figure 1(a) shows a significantly improved overall survival (p = 0.046) for patients with early onset OTC. Figure 1(b) shows no difference in OTC recurrence between patients with typical and early onset OTC.

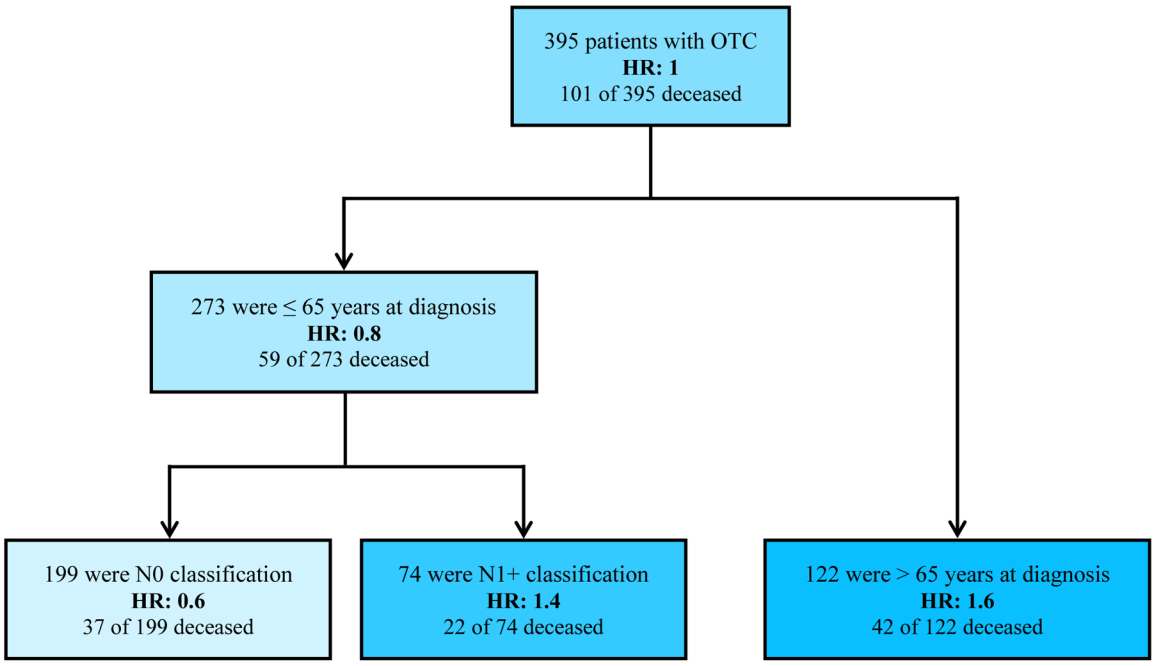



**Fig. 2.**

Predictive model of overall survival using recursive portioning analysis. Three subsets of OTC patients were identified and age at OTC diagnosis and N classification were predictive of overall survival. Abbreviations: OTC – oral tongue squamous cell carcinoma; HR – hazard ratio

**Table 1**

Univariate and multivariate analyses of risk factors for early onset OTC.

| Characteristic | Typical onset<br>No. patients = 282<br>No. patients (% of typical) | Early onset<br>No. patients = 113<br>No. patients (% of early) | OR (95% CI) | P value | aOR (95% CI) | Adjusted p value |
|---|---|---|---|---|---|---|
| **Age at diagnosis (yrs)** | | | | | | |
| Median (IQR) | 63 (58–70) | 42 (36–45) | | | | |
| ***Gender*** | | | | | | |
| Male | 171 (60.6) | 67 (59.3) | ref | | ref | |
| Female | 111 (39.4) | 46 (40.7) | 1.1 (0.7–1.7) | 0.805 | 1.0 (0.5–1.7) | 0.898 |
| ***Race*** | | | | | | |
| White | 265 (94.0) | 111 (98.2) | ref | | ref | |
| African American or Black | 10 (3.6) | 1 (0.9) | 0.2 (0.1–1.9) | 0.175 | - | - |
| Asian | 6 (2.1) | 1 (0.9) | 0.4 (0.1–3.3) | 0.396 | 0.2 (0.1–2.2) | 0.207 |
| American Indian/AK native | 1 (0.4) | 0 | - | - | - | - |
| Native Hawaiian | 0 | 0 | - | - | - | - |
| **Clinical Stage** | | | | | | |
| **T** | | | | | | |
| T1 | 110 (39.0) | 44 (38.9) | ref | | | |
| T2 | 90 (31.9) | 41 (36.3) | 1.1 (0.7–1.9) | 0.616 | | |
| T3 | 41 (14.5) | 14 (12.4) | 0.9 (0.4–1.7) | 0.658 | | |
| T4[a] | 18 (6.4) | 4 (3.5) | 0.6 (0.2–1.7) | 0.312 | | |
| TX | 18 (6.4) | 10 (8.9) | 1.4 (0.6–3.2) | 0.448 | | |
| Missing | 5 (1.8) | 0 | - | - | | |
| **N** | | | | | | |
| N0 | 193 (68.4) | 74 (65.5) | ref | | | |
| N1 | 35 (12.4) | 14 (12.4) | 1.0 (0.5–2.0) | 0.902 | | |
| N2a | 2 (0.7) | 1 (0.9) | 1.3 (0.1–14.6) | 0.829 | | |
| N2b | 22 (7.8) | 9 (8.0) | 1.1 (0.5–2.4) | 0.877 | | |
| N2c | 11 (3.9) | 4 (3.5) | 1.0 (0.3–3.1) | 0.930 | | |
| NX | 14 (5.0) | 11 (9.7) | 2.0 (0.9–4.7) | 0.092 | | |

| Characteristic | Typical onset No. patients = 282 No. patients (% of typical) | Early onset No. patients = 113 No. patients (% of early) | OR (95% CI) | P value | aOR (95% CI) | Adjusted p value |
|---|---|---|---|---|---|---|
| Missing | 5 (1.8) | 0 | - | - | | |
| **M** | | | | | | |
| M0 | 258 (91.5) | 99 (87.6) | ref | | | |
| MX | 19 (6.7) | 13 (11.5) | 1.8 (0.9–3.8) | 0.127 | | |
| Missing | 5 (1.8) | 1 (0.9) | - | - | | |
| ***Overall***[b] | | | | | | |
| I | 102 (36.2) | 41 (36.3) | ref | | ref | |
| II | 67 (23.8) | 25 (22.1) | 0.9 (0.5–1.7) | 0.803 | 0.9 (0.4–1.9) | 0.771 |
| III | 45 (16.0) | 20 (17.7) | 1.1 (0.6–2.1) | 0.758 | 1.0 (0.4–2.2) | 0.908 |
| IVA | 45 (16.0) | 16 (14.2) | 0.9 (0.5–1.7) | 0.722 | 0.7 (0.3–1.8) | 0.473 |
| IVB | 1 (0.4) | 0 | - | - | - | - |
| Missing | 22 (7.8) | 11 (9.7) | - | - | - | - |
| **Grade** | | | | | | |
| I: Well differentiated | 58 (20.6) | 25 (22.1) | 1.1 (0.6–1.9) | 0.691 | | |
| II: Moderately differentiated | 166 (58.9) | 64 (56.6) | ref | | | |
| III: Poorly differentiated | 33 (11.7) | 13 (11.5) | 1.0 (0.5–2.1) | 0.952 | | |
| Non-high grade | 25 (8.9) | 11 (9.7) | 1.1 (0.5–2.5) | 0.735 | | |
| ***Treatment*** | | | | | | |
| Surgery only | 171 (60.6) | 59 (52.2) | ref | | ref | |
| Surgery + chemoradiation | 54 (19.2) | 24 (21.2) | 1.3 (0.7–2.3) | 0.379 | 1.2 (0.5–2.6) | 0.661 |
| Surgery + radiation | 30 (10.6) | 21 (18.6) | **2.0 (1.1–3.8)** | **0.028** | **2.7 (1.2–6.3)** | **0.019** |
| Other[c] | 27 (9.6) | 9 (8.0) | 1.0 (0.4–2.2) | 0.934 | 1.4 (0.5–4.0) | 0.498 |
| ***Alcohol Use at Diagnosis***[d] | | | | | | |
| None | 74 (26.2) | 33 (29.2) | ref | | ref | |
| Light | 67 (23.8) | 26 (23.0) | 0.9 (0.5–1.6) | 0.656 | 1.0 (0.5–2.2) | 0.980 |
| Mild to moderate | 70 (24.8) | 37 (32.7) | 1.2 (0.7–2.1) | 0.560 | 1.3 (0.6–2.8) | 0.452 |
| Heavy[g] | 37 (13.1) | 5 (4.4) | **0.3 (0.1–0.8)** | **0.022** | 0.4 (0.1–1.2) | 0.100 |
| Missing | 34 (12.1) | 12 (10.6) | - | - | - | - |

| Characteristic | Typical onset No. patients = 282 No. patients (% of typical) | Early onset No. patients = 113 No. patients (% of early) | OR (95% CI) | P value | aOR (95% CI) | Adjusted p value |
|---|---|---|---|---|---|---|
| Drinks per week, Median (IQR) | 8 (2–20)[f] | 4 (2–6)[g] | | | | |
| **Past Alcohol Use**[d] | | | | | | |
| None | 72 (25.5) | 32 (28.3) | ref | | | |
| Light | 32 (11.4) | 13 (11.5) | 0.9 (0.4–2.0) | 0.818 | | |
| Mild to moderate | 56 (19.9) | 28 (24.8) | 1.1 (0.6–2.1) | 0.708 | | |
| Heavy[g] | 61 (21.6) | 20 (17.7) | 0.7 (0.4–1.4) | 0.362 | | |
| Missing | 61 (21.6) | 20 (17.7) | - | - | | |
| Drinks per week, Median (IQR) | 24 (10–40)[h] | 18 (9–36)[i] | | | | |
| **Reported Tobacco Use** | | | | | | |
| Never | 90 (31.9) | 52 (46.0) | **1.8 (1.2–2.8)** | **0.009** | | |
| Ever[j] | 192 (68.1) | 61 (54.0) | ref | | | |
| **Reported Smoking Tobacco Use**[k] | | | | | | |
| No | 100 (35.5) | 61 (54.0) | **2.1 (1.4–3.3)** | **0.001** | | |
| Yes | 182 (64.5) | 52 (46.0) | ref | | | |
| ***Cigarette Use*** | | | | | | |
| Never | 107 (37.9) | 63 (55.8) | ref | | ref | |
| Former | 95 (33.7) | 23 (20.4) | **0.4 (0.2–0.7)** | **0.002** | **0.5 (0.2–0.9)** | **0.034** |
| Current | 80 (28.4) | 27 (23.9) | **0.6 (0.3–0.9)** | **0.042** | 0.7 (0.4–1.4) | 0.350 |
| Pack-years, Median (IQR) | 42 (30–63)[l] | 20 (11.5–36)[m] | | | | |
| **Reported Cigar Use** | | | | | | |
| No | 250 (88.7) | 103 (91.2) | ref | | | |
| Yes | 32 (11.4) | 10 (8.9) | 0.8 (0.4–1.6) | 0.468 | | |
| Cigar-years, Median (IQR) | 45 (12.9–294)[n] | 6 (1–15)[o] | | | | |
| **Reported Pipe Use** | | | | | | |
| No | 265 (94.0) | 111 (98.2) | ref | | | |
| Yes | 17 (6.0) | 2 (1.8) | 0.3 (0.1–1.2) | 0.093 | | |

| Characteristic | Typical onset No. patients = 282 No. patients (% of typical) | Early onset No. patients = 113 No. patients (% of early) | OR (95% CI) | P value | aOR (95% CI) | Adjusted p value |
|---|---|---|---|---|---|---|
| Pipe-years, Median (IQR) | 4.5 (3–30)[p] | 5.5 (5–6)[q] | | | | |
| **Reported Smokeless Tobacco Use**[r] | | | | | | |
| No | 250 (88.7) | 93 (82.3) | ref | | | |
| Yes | 32 (11.4) | 20 (17.7) | 1.7 (0.9–3.1) | 0.094 | | |
| ***Reported Snuff Use*** | | | | | | |
| No | 274 (97.2) | 99 (87.6) | ref | | ref | |
| Yes | 8 (2.8) | 14 (12.4) | **4.8 (2.0–11.9)** | **0.001** | **5.4 (1.8–15.8)** | **0.002** |
| Can-years, Median (IQR) | 18 (5–30)[s] | 9.5 (2–20)[t] | | | | |
| **Reported Chewing Tobacco Use** | | | | | | |
| No | 257 (91.1) | 99 (87.6) | ref | | | |
| Yes | 25 (8.9) | 14 (12.4) | 1.5 (0.7–2.9) | 0.291 | | |
| Pouch-years, Median (IQR) | 6.75 (1.4–20)[u] | 11 (2–14)[v] | | | | |
| **Reported Illicit Drug Use** | | | | | | |
| No | 201 (71.0) | 76 (67.3) | ref | | | |
| Yes | 17 (6.0)[w] | 12 (10.6)[x] | 1.9 (0.9–4.1) | 0.119 | | |
| Missing | 65 (23.0) | 25 (22.1) | - | - | | |
| **Highest Education Level** | | | | | | |
| < HS | 29 (10.3) | 4 (3.5) | 0.4 (0.1–1.1) | 0.061 | | |
| HS | 98 (34.8) | 39 (34.5) | ref | | | |
| College | 57 (20.2) | 30 (26.6) | 1.3 (0.7–2.4) | 0.342 | | |
| Graduate | 15 (5.3) | 11 (9.7) | 1.8 (0.8–4.4) | 0.165 | | |
| Post-Grad | 15 (5.3) | 4 (3.5) | 0.7 (0.2–2.2) | 0.500 | | |
| Missing | 68 (24.1) | 25 (22.1) | - | - | | |

Italicized variables were included in the multivariate analysis

Abbreviations: OR – odds ratio; aOR – adjusted odds ratio; CI – confidence interval; IQR – interquartile range

[a] Contains 2 patients listed as “T4”, 19 patients listed as “T4a”, and 1 patient listed as “T4b”

[b] 13 patients (8 typical, 5 early) with only T and N stages were given an overall classification assuming no distant metastases (M0)

[c] Surgery and induction chemotherapy followed by chemoradiation (N=8), chemoradiation (N=6), induction chemotherapy followed by chemoradiation (N=5), palliative care (N=3), radiation only (N=3), surgery with induction chemotherapy (N=3), chemotherapy only (N=2), surgery with chemotherapy (N=2), chemotherapy followed by chemoradiation (N=1), chemotherapy followed by radiation (N=1), induction chemotherapy (N=1), surgery with induction chemotherapy and radiation (N=1),

[d] None: <12 drinks lifetime; Light: >12 weeks lifetime but 0 drinks/week; Mild to moderate: <8 drinks/week (F) or <15 drinks/week (M); Heavy: >=8 drinks/week (F) or >=15 drinks/week (M)

[e] Patient labeled as heavy alcohol use if specified 'heavy use', 'significant use', 'a lot', 'alcohol abuse', or 'alcoholism'

[f] 82 typical onset mild to moderate and heavy alcohol users

[g] 37 early onset mild to moderate and heavy alcohol users

[h] 49 typical onset mild to moderate and heavy alcohol users

[i] 25 early onset mild to moderate and heavy alcohol users

[j] Defined as former/current cigarette smoker or reported user of cigars, pipes, snuff, or chewing tobacco

[k] Cigarette, cigar, or pipe use

[l] 138 typical onset former or current cigarette users

[m] 42 early onset former or current cigarette users

[n] 21 typical onset cigar users

[o] 5 early onset cigar users

[p] 9 typical onset pipe users

[q] 2 early onset pipe users

[r] Snuff or chewing tobacco use

[s] 5 typical onset snuff users

[t] 10 early onset snuff users

[u] 10 typical onset chewing tobacco users

[v] 6 early onset chewing tobacco users

[w] Marijuana (N=15), cocaine (N=5), LSD (N=2)

[x] Marijuana (N=9), cocaine (N=4), methamphetamine (N=1)

## Table 2

Cox proportional hazards model, overall survival and recurrence.

| **Survival, all-cause mortality** | | | | |
|---|---|---|---|---|
| **Onset** | **Hazard ratio (95% CI)** | **P value** | **Adjusted hazard ratio[a] (95% CI)** | **P value** |
| Typical | ref | - | - | - |
| Early | 0.7 (0.5–1.1) | 0.133 | **0.6 (0.3–0.9)** | **0.046** |
| **OTC recurrence[b]** | | | | |
| **Onset** | **Hazard ratio (95% CI)** | **P value** | **Adjusted hazard ratio[a] (95% CI)** | **P value** |
| Typical | ref | - | - | - |
| Early | 1.0 (0.7–1.4) | 0.962 | 0.8 (0.5–1.3) | 0.307 |

Abbreviations: OTC – oral tongue squamous cell carcinoma; CI – confidence interval

[a]Adjusted for sex, race, overall clinical stage, treatment, alcohol use at diagnosis, and ever v. never tobacco use

[b]Three patients with diffuse distant recurrence were assessed radiographically only. If no exact end of treatment date was found in the EHR, the treatment end date was assumed to be the 1st of month (N=7). If no exact recurrence date was found in the EHR, the date of recurrence was assumed to be the 1st of month (N=1). If there was unclear treatment response, OTC recurrence was assumed if specified as such in the physician note.