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Association of metropolitan residential status on survival from tongue cancer (2010- 2015): A SEER Study

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2017

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Rollins School of Public Health of Emory University

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Abstract

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Background: The incidence of squamous cell carcinoma of the tongue has increased over the years in the US. Living in non-metropolitan areas has shown a better prognosis and long-term survival in patients with oral cavity squamous cell carcinoma compared to their metropolitan counterparts in some studies. To further explore this phenomenon, we sought to examine the association between survival from squamous cell cancer of the oral tongue and metropolitan residential status at the time of diagnosis in a population-based US cohort.

Methods: We identified 5,761 cases diagnosed with squamous cell carcinoma (OSCC) of the oral tongue between the years 2010 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. Cases were categorized by their age, sex, race, poverty, marital status, stage at diagnosis, grade of the carcinoma (differentiation), surgical procedure, chemotherapy, and radiation therapy. We examined the metropolitan versus non-metropolitan residential status differences in survival using Cox regression model while controlling for potential confounders.

Results: Eighty-eight percent of our final cohort were from metropolitan areas while only twelve percent were from non-metropolitan areas. The study cohort was predominantly comprised of white individuals and had more males than females. About half of the cohort was diagnosed with early-stage cancer (stage I and II), and the other half included late stage (stage III and IV) and unknown stages. Relative to non-metropolitan areas, metropolitan areas comprised a larger proportion of non-white cancer patients, had fewer patients living below the poverty line and had a slightly larger patient population that received chemotherapy. Kaplan-Meier survival curves and Cox regression modeling showed no statistically significant association between survival and metropolitan residential status (HR=0.99, 95% CI: (0.92,1.08)). Increasing stage and grade were the strongest predictors of poor outcomes along with receipt of non-surgical therapies.

Conclusions: The findings of this study, conducted in a large US population-based registry cohort, do not show evidence of an association between metropolitan residential status and survival from oral tongue cancer as observed in other studies on oral cancer. Further research should be conducted to explore the pathways more fully through which residential status can lead to differences in cancer outcomes.

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Chapter I: Background

Cancer is a major public health crisis with an estimated 19.3 million new cancer cases and about 10 million cancer deaths in the year 2020. The global cancer burden is growing and is expected to reach 28.4 million cases by 2040, representing a 47% increase from 2020 (1,2). In the United States, 22.5% of all deaths are due to malignant neoplasms. Overall, cancer is the second most common cause of death in the US and the leading cause of death among Americans between the age of 35-64 years (3,4).

Head and Neck Cancer

Head and neck cancer (HNC) are composed of malignancies that arise in the epithelial surface of the upper aerodigestive tract. Major anatomic sites for development of cancer within the head and neck include the oral cavity, pharynx, larynx, paranasal sinuses, and salivary glands (5). HNC accounts for more than 650,000 cases and 330,000 deaths annually across the globe (6). In the US, it accounts for about 3-4 percent of all malignancies, with approximately 66,000 patients being diagnosed and 14,600 succumbing to this cancer annually (7,8). The incidence of HNC is markedly higher in men compared to women. The primary risk factors associated with developing HNC are tobacco use and drinking alcohol. Other risk factors include betel quid, poor oral hygiene, occupational exposure, radiation exposure, viral infection with either Epstein-Barr Virus (EBV) or Human Papilloma Virus (HPV), and family history (8).

Oral Cavity Cancer

Oral cavity cancers represent approximately 85% of the HNCs and include tumors of the lips, cheeks, gums, vermillion border, floor of the mouth and palate, and the anterior two-thirds of the tongue (9-12). According to the National Institute of Dental Craniofacial Research (NIH), about

10.5 adults per 100,000 develop oral cancers annually. Predominate histologic types of oral and pharyngeal cancers include squamous cell carcinoma, verrucous carcinoma, minor salivary gland carcinoma (adenoid cystic carcinoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma), sarcoma, and lymphomas (10). The main risk factors for oral cancer include tobacco and alcohol use which have a direct carcinogenic effect on oral tissue (11). HPV infection of the mouth and throat is also considered to increase the risk for developing this cancer as with other cancers of the head and neck (12). The incidence rate of oral cancers in men is twice that of women. Between 1973 to 1996, there was an increasing trend of oral cancer among older African American men and young white women (13,14). From 2007 to 2016, the incidence rates decreased by 1-2 % per year in African American men and women but increased by about 1% in non-Hispanic white men and women (12). However, the survival rates of oral cancer have remained stable. Reports by the National Cancer Institute suggest that overall, only 65% of people with oral cancer survive beyond 5 years. Diagnosing oral cancer at an early stage significantly increases 5-year survival rates when compared to patients diagnosed at late stages. Unfortunately, only 29% of cases are diagnosed at a local stage for which the 5-year survival is highest at 84 percent. The 5-year relative survival rate of cancers of the oral cavity is much lower in African American populations (48%) than in whites (67%) (12, 15).

According to a few studies, African American populations and Hispanics were more likely to present with later stages of oral cavity squamous cell cancer (OSCC), compared to white populations. This later stage at diagnosis contributed to greater mortality in African American populations. These studies showed no statistically significant difference in mortality for Hispanics versus whites or Asians versus whites (16, 17). Reports from the Surveillance, Epidemiology, and End Results (SEER) Program reveal that the rate of new cases of oral and pharyngeal cancer was 11.4 per 100,000 per year and the death rate was 2.5 per 100,000 per year. Rates were age adjusted and were based on 2013-2017 incident diagnoses and 2014-2018 deaths. The percent of deaths were highest among people aged 65-74 (15).

A study by Johnson et al used the 2008 NHIS data to evaluate the association between oral cancer screening and socioeconomic factors like education, income, and health insurance (18). Their study showed a statistically significant correlation of these factors with awareness oral cancer screening. This study indicated that awareness of oral cancer screening increased with higher education levels. People with less than a 9th grade education had significantly lower odds of being aware (or having knowledge about the importance of) about oral cancer screening compared to people with a college degree. The study also found a significant correlation between income and health insurance with oral cancer screening and awareness. It was observed that with higher income and having a private health insurance, there was an increased awareness to get screened for oral cancer.

Oral Tongue Cancer

Oral Tongue Cancer (OTC) represents malignancies that develop in a distinct subsite within the oral cavity. These cancers have a distinct behavior and prognosis compared to other subsites within the oral cavity due to differences in anatomy and lymphatic drainage. Anatomically, the oral tongue is the anterior two-thirds of the tongue and performs a vital role in eating, speaking, and breathing. OTC is ranked 19th in common types of cancer in the US and represents 1 percent of all new cancer cases based on data from 2011-2017 (19). The incidence of SCC of the oral tongue has been increasing since 2001 (19, 20). Based on data from the SEER Program, the incidence rate of oral tongue cancer was 3.5 per 100,000 per year and the death rate was 0.7 per 100,000 per year. These rates are age-adjusted and based on 2013-2017 cases and 2014-2018 deaths. Tobacco use, heavy alcohol use, and infection with human papillomavirus (HPV) are also the known risk factors associated with this cancer (20,21).

Between 1975 and 2007, SCC of the oral tongue has been increasing among white individuals between the age of 18-44 years, especially among white women (14). Despite the rising increase of these cancers in young individuals, some studies have demonstrated that young patients have improved survival rates compared to older patients (14,22,23). The increase in incidence of tongue cancers is showing improving prognosis irrespective of the treatment received, warranting further clinical research and investigation (24,25). In a study conducted using SEER data where the patients were stratified by age (> 40 and <40 years) and sex, younger female patients had a better overall survival compared to young male patients (75% vs 67% at 5 years), both of which were better than corresponding survival in older patients (22). Younger patients in general had a better prognosis compared to older patients as younger patients were more likely to receive surgery or a combination of surgery and radiation as a mode of treatment, hence improving their prognosis. Multivariate analysis was performed in this study and results demonstrated that tumor stage was associated with worse overall survival while surgical treatment predicted better outcomes in all groups except young females. Higher tumor grade resulted in worse overall survival in older patients but not younger ones.

The 5-year relative survival of oral tongue cancer in the US between 2010-2016 was 65 percent (20). Early diagnosis is of vital importance because treatment in those cases causes less harm relatively. As many as 25% of patients with tongue cancer have neck metastasis which affects prognosis (21, 23). In a study conducted using data from the National Cancer Database on cases diagnosed between 2004 and 2013 with pathologic stage T2N0 oral tongue cancer with negative surgical margins, there was no survival benefit observed for patients receiving post-operative radiation therapy versus surgery alone (26).

Despite an overall improvement in cancer survival due to earlier diagnosis and better treatment, residents living in more disadvantaged areas show lower survival compared to those living in less disadvantaged areas (27). There have been multiple studies looking at the role of residential status and cancer incidence and outcomes in general (28-31). One of the studies was conducted by the Centers for Disease Control and Prevention (CDC) using data from the National Program of Cancer Registries combined with data from the SEER registries. This study showed that Americans living in non-metropolitan areas tend to develop cancer less often compared to their metropolitan counterparts but were more likely to die of the disease (32). The authors discussed that differences between metropolitan and non-metropolitan counties in cancer incidence might be due to differences in risk factors like cigarette smoking, obesity, and physical inactivity, whereas differences in cancer deaths might be due to disparities in access to healthcare and timely diagnosis and treatment. In another study on cancer trends and incidence using data from the North American Association of Central Cancer Registries for the period 1975 to 2013, cancer incidence rates were generally higher in urban populations relative to rural populations, except for the South, although the urban decline in incidence rate was greater than in rural populations (10.2% vs. 4.8%, respectively) (33). This study did not look at cancer outcomes.

The literature is more limited on studies around metropolitan residential status and outcomes specific to cancers of the head and neck. One study by Amrita Mukherjee and colleagues using electronic medical records from a National Cancer Institute designated cancer center in Alabama suggested that outcomes of these cancers are generally poor, regardless of residential status, because the majority of patients present at the clinic with later stage (III/IV) of disease (34). In a recent analysis on geographic location and oral cavity squamous cell cancer (OSCC)in the US using SEER data, study results suggested that individuals residing in rural areas at the time of diagnosis experienced better overall survival relative to those in urban areas (HR=0.87; 95% CI: 0.83,0.92). Despite this finding, these authors also noted that outcomes remained poor in both residential groups (28). Understanding differences in age, gender, race, and other factors based on residency is important when targeting early intervention strategies for HNC. Certain individuals may have different behavior patterns (e.g., smoking, drinking, and sexual practices) in urban and rural settings that may make them more susceptible to developing HNC (32, 34) and ultimately experiencing different outcomes as well.

Cancers of the oral tongue have been grouped together with all other cancers of the oral cavity (buccal, palate, mandible, floor of mouth) in the limited studies conducted to date on residential status and outcomes. While these cancers do share common risk factors, published outcomes are not homogeneous within this group of cancers. To our knowledge, there have been no studies exploring residential status and its effects on survival from oral tongue cancer specifically. Keeping this gap in mind, the purpose of this study is to explore the association residential status and survival outcomes from oral tongue cancer, while controlling for potential confounders.

Chapter II: Manuscript

Association of metropolitan residential status on survival from tongue cancer (2010- 2015): A SEER Study

Author(s): Varsha Natarajan, Kevin C. Ward, Brian J. Boyce

The incidence of squamous cell carcinoma of the tongue has increased over the years in the US. Living in non-metropolitan areas has shown a better prognosis and long-term survival in patients with oral cavity squamous cell carcinoma compared to their metropolitan counterparts in some studies. To further explore this phenomenon, we sought to examine the association between survival from squamous cell cancer of the oral tongue and metropolitan residential status at the time of diagnosis in a population-based US cohort.

We identified 5,761 cases diagnosed with squamous cell carcinoma (OSCC) of the oral tongue between the years 2010 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. Cases were categorized by their age, sex, race, poverty, marital status, stage at diagnosis, grade of the carcinoma (differentiation), surgical procedure, chemotherapy, and radiation therapy. We examined the metropolitan versus non-metropolitan residential status differences in survival using Cox regression model while controlling for potential confounders.

Eighty-eight percent of our final cohort were from metropolitan areas while only twelve percent were from non-metropolitan areas. The study cohort was predominantly comprised of white individuals and had more males than females. About half of the cohort was diagnosed with early-stage cancer (stage I and II), and the other half included late stage (stage III and IV) and unknown stages. Relative to non-metropolitan areas, metropolitan areas comprised a larger proportion of non-white cancer patients, had fewer patients living below the poverty line and had a slightly larger patient population that received chemotherapy. Kaplan-Meier survival curves and Cox regression modeling showed no statistically significant association between survival and metropolitan residential status (HR=0.99, 95% CI: (0.92,1.08)). Increasing stage and grade were the strongest predictors of poor outcomes along with receipt of non-surgical therapies.

The findings of this study, conducted in a large US population-based registry cohort, do not show evidence of an association between metropolitan residential status and survival from oral tongue cancer as observed in other studies on oral cancer. Further research should be conducted to explore the pathways more fully through which residential status can lead to differences in cancer outcomes.

Introduction

Oral tongue cancers (OTC) represent malignancies that develop in a distinct subsite within the oral cavity. These cancers have a unique behavior and prognosis compared to other subsites within the oral cavity due to differences in anatomy and lymphatic drainage. OTC is ranked 19th in common types of cancer in the US and represents 1 percent of all new cancer cases. The most common histologic type of OTC is squamous cell carcinoma (SCC) (20). The incidence of squamous cell carcinoma of the oral tongue has been increasing since 2001 (20).

The risk factors for oral tongue cancer (OTC) includes tobacco and heavy alcohol use along with infection due to Human Papilloma Virus (HPV) especially HPV type 16 (11, 20). OTC is more common in males compared to females. Based on 2014-2018 reports by SEER, the rate of new cases of OTC was 5.4 per 100,000 in males while it was 2.0 per 100,000 in females (20). Age-adjusted incidence rates have been rising on average 2.2% each year over 2009–2018 and these cancers are most frequently diagnosed among people between the ages of 55 and 64 years. As expected, mortality increases with age with the percent of deaths highest among people aged 65-74 years. The death rate observed in males is 1.0 per 100,000 while it is much lower in females at 0.4 per 100,000(20). The 5-year relative survival of oral tongue cancer in the US between 2010-2016 was 65 percent (20).

According to previously published literature, socioeconomic factors like education, income, health insurance, and immigration status have shown a significant association with oral cancer screening and awareness (18). There have been multiple studies looking at the role of residential status and cancer incidence and outcomes in general (28-31), but the literature is more limited on studies around residential status and outcomes specific to cancers of the head and neck. In a recent analysis on geographic location and oral cavity squamous cell cancer (OSCC) in the US using SEER data, study results suggested that individuals residing in rural areas at the time of diagnosis experienced better overall survival relative to those in urban areas (HR=0.87; 95% CI: 0.83,0.92). Despite this finding, the authors noted that outcomes remained poor in both residential groups (28). Understanding differences in age, gender, race, and other factors based on residency is important when targeting early intervention strategies for cancers of the oral cavity. Certain individuals may have different behavior patterns (e.g., smoking, drinking, and sexual practices) in urban and rural settings that may make them more susceptible to developing these cancers (32, 34) and ultimately experiencing different outcomes as well.

Cancers of the oral tongue have been grouped together with all other cancers of the oral cavity (buccal, palate, mandible, floor of mouth) in the limited studies conducted to date on residential status and outcomes. While these cancers do share common risk factors, published outcomes are not homogeneous within this group of cancers. To our knowledge, there have been no studies exploring residential status and its effects on survival from oral tongue cancer specifically. Keeping this gap in mind, the purpose of this study is to explore the association residential status and survival outcomes from oral tongue cancer, while controlling for potential confounders.

Methods

This is a retrospective, population-based analysis based on Surveillance, Epidemiology, and End Results (SEER) data which aims to determine the association between metropolitan residential status and survival of squamous cell carcinoma of the oral tongue.

Study Population

The SEER program collects data from 18 population-based cancer registries which account for about 36% of the US population. For this analysis, all cases aged 18 years and above with squamous cell carcinoma of the tongue diagnosed between the year 2010 and 2015 were selected. Cases had International Classification of Disease for Oncology (ICD_O) primary site codes of ‘C02.0- Dorsal surface of tongue, NOS’, ‘C02.1- Border of tongue’, ‘C02.2- Ventral surface of tongue, NOS’, ‘C02.3- Anterior two-thirds of tongue, NOS’, ‘C02.8- Overlapping lesion of tongue’ and ‘C02.9- Tongue, NOS’. Cancers involving the base of tongue and lingual tonsil were excluded because they are located at a different anatomic site called the oropharynx and have a distinct biology and prognosis compared to OTCs.

Primary Exposure

The primary independent variable was a bivariate classification of cancer patient residential counties at the time of their diagnosis into metropolitan versus non-metropolitan areas. This variable was constructed using USDA Economic Research Service Rural Urban Continuum Codes from 2013 (36). The Rural Urban Continuum codes were developed in 1974 and are updated every 10 years. The 2013 Rural Urban Continuum codes distinguish metropolitan counties by the population size of the metropolitan area, and non-metropolitan counties by degree of urbanization and adjacency to a metropolitan area. They contain 9 categories but were broadly grouped for this study into metropolitan (codes 1-3) vs non-metropolitan areas (codes 4-9).

Outcome Measure

The dependent variable for this analysis was 5-year cause specific survival, with cause of death obtained from SEER data. SEER registries link their data annually with state vital records and the National Death Index to obtain date of death and cause of death. Survival time was defined as the number of months from the date of diagnosis until death from OTC, 5-years, or censoring.

Survival time was censored at the time of death from another cause, when a patient was lost to follow up, or at the study endpoint of December 31st, 2016.

Covariates

Other covariates of interest include stage of the carcinoma at diagnosis which is a SEER variable combining clinical and pathologic data. Stage was classified into 8 groups- “Stage 1”, “Stage 2”, “Stage 3”, “Stage 4a”, “Stage 4b”, “Stage 4c”, “Stage 4 NOS” and “Unknown”. Poverty status was categorized into three groups- “less impoverished (0-9.99%)”, “more impoverished (10-19.99%)” and “most impoverished (>20%)”. This variable is an area-based measure of poverty that uses data from the patient’s residential address at the time of diagnosis and links the corresponding census tract of the patients’ residence to US census data on poverty. Treatment variables included the type of surgical treatment received (like wide excision, local excision of tumor and surgery not otherwise specified) along with chemotherapy and radiation received (“yes” vs “no/unknown”). Each case included in the study was further categorized according to age, race, sex, marital status, and grade of the carcinoma.

Statistical Analysis

Distribution of study covariates were presented as counts and percentages across the primary exposure i.e., metropolitan vs non-metropolitan residential status. Differences in covariate distributions were determined using a Chi-square test, with an alpha of 0.05.

The survival for oral tongue cancer patients was analyzed by constructing Kaplan-Meier curves with their corresponding log-rank tests for statistical significance to see the patient survival according to metropolitan residential status. A multivariable Cox proportional hazards model was used to examine the association between survival and metropolitan residential status, controlling for other covariates. Age, race, poverty, and stage of diagnosis are known confounders for survival from OTC based on the literature. We performed confounding assessment for all other covariates and chose to retain them all in our multivariate model. Multivariable survival results were shown as adjusted hazard ratios (HRs) reported along with their 95% confidence intervals. Proportional hazard assumptions were tested by graphical and goodness of fit tests for each variable present in the model.

All analyses were performed using SAS statistical software 9.4. For all the analyses, the cut point for statistical significance was a two-sided alpha error of 0.05.

Results

There was a total of 66,726 observations with oral and pharyngeal cancer in the SEER database out of which 5,761 cases were reported with squamous cell carcinoma of the oral tongue diagnosed between the year 2010 and 2015 aged 18 years and above. As seen in Table 1, 88% of the total cases resided in metropolitan areas at the time of diagnosis. Approximately two-thirds of the total cases were aged 55 years and above. The study cohort was predominantly comprised of white individuals (85%) and had more males than females. About half the cohort was married and 14.3% belonged to the most impoverished group (poverty greater than 20%).

Roughly half of the cases were diagnosed at an early stage of the disease (stage I and stage II) and the other half included cases diagnosed at a late stage (stage III and stage IV) and the unknown stages. Three-fourths of the study group had Grade 1 or 2 carcinoma, corresponding to well or moderately differentiated carcinoma respectively. Approximately three-fourth of the total cases underwent wide or radical excision of tumor and one-fourth of the cohort received chemotherapy as treatment and 40% received radiation therapy. Most of the variables in the analysis had similar distributions across the metropolitan and non-metropolitan residential status groups. Relative to non-metropolitan areas however, metropolitan areas comprised a larger proportion of non-white cancer patients, had fewer patients living below the poverty line and had a slightly larger patient population that received chemotherapy.

Survival Analysis

Kaplan-Meier curves show that survival was not significantly different across the metropolitan vs non-metropolitan groups with a log-rank p-value=0.9313 (Figure 1). The results of the survival analysis using a Cox proportional hazard model are shown in the Table 2. Non-metropolitan resident status showed a hazard ratio (HR) close to 1.0 indicating there was no effect of resident status with survival from OTC in these data. The risk of mortality increased with age, but no differences were observed by race and sex. The most impoverished group (poverty >20%) didn't have a difference in the mortality either, with a HR of 1.04 (95% CI: 0.95, 1.15). Married people showed a significantly decreased risk of mortality compared to unmarried individuals.

As expected, the HR increased with each increasing stage group. Members of the cohort with Stage IVA disease had a HR of 1.90 (95% CI: 1.73, 2.08) while those with stage IVC had a HR of 4.01 (95% CI: 3.18, 5.06) relative to those with stage I disease. Similarly, grade 3 or grade 4 carcinoma, corresponding to poorly or undifferentiated carcinoma respectively, showed a higher risk of mortality compared to early grade (1 or 2) carcinomas. Stage and grade of the carcinoma were both very strong predictors associated with poor outcomes. For treatment variables, wide or radical excision of tumor showed 40% reduced mortality compared to the local excision of tumor with a HR of 0.61 (95% CI: 0.56, 0.67). There was an increased risk of OTC death observed with those who were the recipients of non-surgical treatments like chemotherapy and radiation therapy. Chemotherapy and radiation therapy showed increased mortality with HR of 1.28 (95% CI: 1.21, 1.36) and 1.16 (95% CI: 1.10, 1.22) respectively.

Discussion

In this population-based cohort of patients having squamous cell carcinoma of the oral tongue diagnosed between the year 2010 and 2015, we found no association between metropolitan status and survival from oral tongue cancer with HR of 0.99 (95% CI: 0.92, 1.08). These findings were not consistent with the previous study exploring rural patients with oral squamous cell carcinoma (28). In the rural (non-metropolitan) patients study, the non-metropolitan subgroup was more likely to present at the time of diagnosis with an earlier stage and lower grade carcinoma. They exhibited superior overall survival compared to the urban (metropolitan) subgroup (28, 37).

There have been studies showing a relationship of age and survival, which can be seen in this study as well, with higher relative mortality in increasing age groups. We also found a positive association with better survival outcomes among married individuals. This is consistent with a wide body of literature on this topic which often attributes this association to the impact of social support within married couples. With race, the association between OTC and survival was not statistically significant contrary to studies published previously. In previous literature, it has been reported that African American oral cancer patients are more likely to be diagnosed with advanced stage, though many studies also found that disparities in race in survival remained even after controlling for stage at diagnosis (38-40). In our study, survival from oral tongue cancer by sex was also not different in males and females. Poverty status also did not show a significant relationship with survival in our data, but in other studies, lower socioeconomic status is a strong determinant for cancer, stage of cancer and survival (40).

As seen in previous studies, early-stage diagnoses and surgical treatment remained significant predictors for survival. This surgical finding was expected as surgery is standard of care treatment in tongue cancer and those with unresectable tumors often have more extensive disease. In this study, patients who were treated with radiation and chemotherapy had poorer outcomes even after controlling for stage. This too was expected as these therapies are often used in higher risk patients with more biologically aggressive disease.

This study has several strengths. To our knowledge, this is the first study to explore an association between metropolitan status and OTC using population-based data from the SEER Program which is known to have a high-quality data on cancer patient survival. The large sample size in the SEER database helps us in studying rare cancers and its associations and allows us to perform multivariable analysis using manually curated covariates. The population-based nature of these data combined across 36% of the US population also makes it easier to generalize our findings. The yielded sample size for this study is large (5,761 cases) indicating more stable results.

As with all studies, limitations do exist and need to be acknowledged. One of the main limitations of this study is the use of county level measures for the metropolitan vs non-metropolitan residential status, as counties are often quite large and can encompass heterogenous populations as it relates to residential status. Coding residential status based on a smaller level geography like census tracts or census block groups would have been preferred but the data were not available. The treatment variables chemotherapy and radiation therapy also have limitations in SEER data. One of the limitations regards the completeness of these variables. If the treatments were captured in SEER, that treatment was most likely received by the patient. If it was not captured in SEER, we do not know for certain if the patient never received the treatment or if the registry missed capturing that treatment. Since we can't distinguish between "no treatment" and "unknown if patients received treatment", the variables were classified as "yes" or "no/unknown" in our analyses. Another limitation with these treatment data is that information is not made available about why a patient did/didn't receive the a given therapy. Finally, this study lacks information on some demographic and clinical information. Unfortunately, we do not have information about an individual's socioeconomic status or health insurance which are important predictors for cancers. Also, SEER registries do not collect information about the risk factors associated with cancer like tobacco consumption.

Despite these limitations, our study is a first of its kind, looking at metropolitan residential status and its association with survival from oral tongue cancer. The findings of this study, conducted in a large US population-based registry cohort, do not show evidence of an association between metropolitan residential status and survival from oral tongue cancer as observed in other studies on oral cancer. Further research should be conducted to explore the pathways more fully through which residential status can lead to differences in cancer outcomes.

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Tables and Figures

Table 1. Distribution of characteristics in the cases having oral squamous cell carcinoma of tongue (SEER 2010-2015)

			N= 5761				
Case Characteristics	**Total**		**Non-metropolitan**		**Metropolitan**		**p-value**
	N	**%**	**N**	**%**	**N**	**%**	
Age							0.1400
18-54 years	1839	31.92	197	28.63	1642	32.37	
55-64 years	1740	30.20	220	31.98	1520	29.96	
>65 years	2182	37.88	271	39.39	1911	37.67	
Sex							0.1094
Male	3388	58.81	424	61.63	2964	58.43	
Female	2373	41.19	264	38.37	2109	41.57	
Race							<.0001
White	4885	84.80	631	91.72	4254	83.86	
African American	317	5.50	26	3.78	291	5.74	
AI/AN/ API[#]	559	9.70	31	4.51	528	10.41	
Person Below Poverty ACS							<.0001
0-9.99%	924	16.04	63	9.16	861	16.97	
10-19.99%	4011	69.62	319	46.37	3692	72.78	
>20%	826	14.34	306	44.48	520	10.25	
Marital Status							0.6376
Not Married	2318	40.24	277	40.26	2041	40.23	
Married	2871	49.84	336	48.84	2535	49.97	
Unknown	572	9.92	75	10.90	497	9.80	
Year of Diagnosis							0.0959
2010	843	14.63	94	13.66	749	14.76	
2011	933	16.20	115	16.72	818	16.12	
2012	956	16.59	101	14.68	855	16.85	
2013	920	15.97	123	17.88	797	15.71	
2014	1018	17.67	140	20.35	878	17.31	
2015	1091	18.94	115	16.72	976	19.24	
AJCC Stage Group 7th Edition							0.2358
Stage I	2058	35.72	244	35.47	1814	35.76	
Stage II	783	13.59	110	15.99	673	13.27	
Stage III	813	14.11	86	12.50	727	14.33	
Stage IV NOS	76	1.32	10	1.45	66	1.30	
Stage IV A	1278	22.18	139	20.20	1139	22.45	

Stage IV B	77	1.34	7	1.02	70	1.38	
Stage IV C	82	1.43	9	1.31	73	1.44	
Unknown Stage	594	10.31	83	12.06	511	10.07	
Grade							0.7888
Grade I and II	4251	73.79	504	73.24	3747	73.86	
Grade III and IV	930	16.14	117	17.01	813	16.03	
Unknown	580	10.07	67	9.74	513	10.11	
Surgery							0.3460
None	958	16.63	121	17.59	837	16.50	
Local tumor destruction and excision	671	11.65	92	13.37	579	11.41	
Wide or radical excision of tumor	4094	71.06	470	68.31	3624	71.44	
Surgery NOS	38	0.66	5	0.73	33	0.65	
Chemotherapy							0.0093
No/ Unknown	4412	76.58	554	80.52	3858	76.05	
Yes	1349	23.42	134	19.48	1215	23.95	
Radiotherapy							0.1841
No/ Unknown	3492	60.61	433	62.94	3059	60.30	
Yes	2269	39.39	255	37.06	2014	39.70	
SEER cause specific death							0.5932
Alive or dead of other causes	4401	76.39	520	75.58	3881	76.50	
Dead (attributable to this cancer dx)	1360	23.61	168	24.42	1192	23.50	

#- American Indian/ Alaska Native/ Asian or Pacific Islander

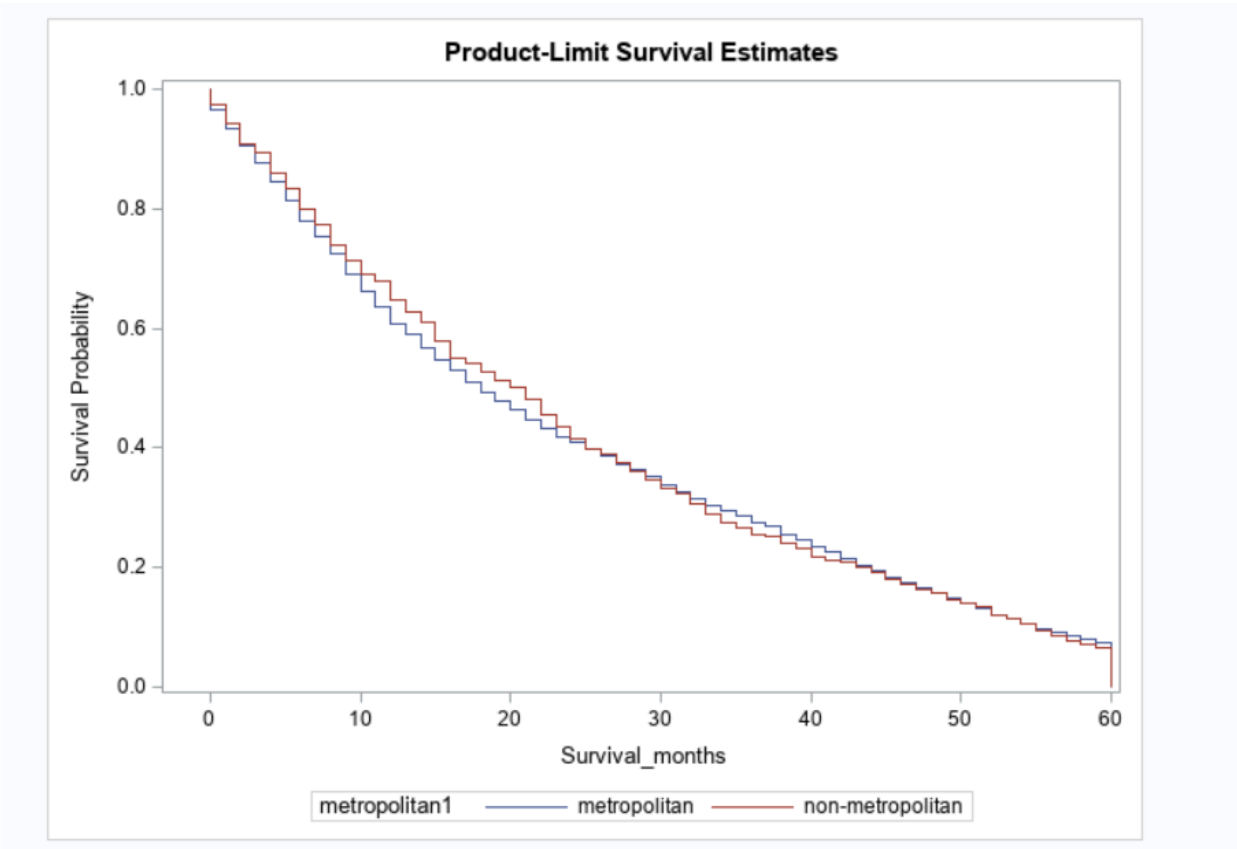
Table 2. Multivariable Cox Proportion Hazard Model for Oral Tongue Cancer, diagnosed from 2010-2015

	Hazard Ratio	95% Confidence Interval	
		Lower limit	Upper limit
Metropolitan Residential Status			
Metropolitan	1.00	Referent	
Non-Metropolitan	0.99	0.92	1.08
Age			
18-54 years	1.00	Referent	
55-64 years	1.09	1.02	1.16
>65 years	1.23	1.15	1.31
Race			
White	1.00	Referent	
African American	1.09	0.97	1.23
AI/AN/API[#]	1.08	0.98	1.18
Stage			
Stage I	1.00	Referent	
Stage II	1.19	1.10	1.30
Stage III	1.44	1.31	1.58
Stage IV NOS	1.79	1.40	2.29
Stage IV A	1.90	1.73	2.08
Stage IV B	2.29	1.80	2.91
Stage IV C	4.01	3.18	5.05
Unknown	1.07	0.97	1.18
Poverty			
0-9.99%	1.00	Referent	
10-19.99%	1.03	0.96	1.11
>20%	1.04	0.95	1.15
Sex			
Male	1.00	Referent	
Female	0.99	0.94	1.04
Marital Status			
Not Married	1.00	Referent	
Married	0.93	0.88	0.99
Unknown	0.93	0.84	1.02
Grade			
Grade 1 or Grade 2	1.00	Referent	
Grade 3 or Grade 4	1.14	1.06	1.23
Unknown	0.84	0.77	0.92
Surgery			

Local tumor destruction and excision	1.00	Referent	
Wide or radical excision of tumor	0.61	0.56	0.67
Surgery NOS	0.63	0.45	0.87
Chemotherapy			
No/ Unknown	1.00	Referent	
Yes	1.28	1.21	1.36
Radiation			
No/Unknown	1.00	Referent	
Yes	1.16	1.10	1.22

#- American Indian/ Alaska Native/ Asian or Pacific Islander

Figure 1. Kaplan-Meier Curve of Survival Probability by Survival Months (N=5,761)



Chapter III: Summary, Public Health Implications, and Possible Future Directions

Oral tongue cancer accounts for about 1% of all new cancer cases in the U.S. It is estimated that there will be 17,960 new cases of OTC and an estimated 2,870 people will die of this disease in 2021. The rate of new cases was 5.4 per 100,000 persons in males while it is 2.0 per 100,000 persons in females in all races. The death rate was 0.7 per 100,000 men and women per year. Approximately 0.4 percent of men and women will be diagnosed with OTC at some point during their lifetime, based on 2016–2018 data. Stage of cancer at diagnosis refers to the extent of cancer in the body, determines treatment protocol, and has a strong influence on the survival. Generally, if the cancer is found only in the part of the body where it started, it is localized. If it spreads to a different part of the body, then the stage is regional or distant. The earlier tongue cancer is detected, there are better chances of a person surviving five years after being diagnosed. For tongue cancer, 29% are diagnosed at the local stage, and the 5-year relative survival for localized tongue cancer is 82.9% (20).

Looking at new cases, deaths, and survival over time (trends) can help one understand whether there is any progress being made and where additional research is needed to address challenges, for example improving screening methods or increasing awareness. Since there have been higher incidence of OTC, increasing awareness and screening for oral tongue cancer should be one of the earliest strategies to be worked upon. This could help in early detection of the cancer and thus treatment would be less invasive and expensive compared to later stages. Screening for cancer can be incorporated as a routine step post-treatment to prevent or detect recurrence as well.

We need to be able to categorize the metropolitan vs non-metropolitan residential status not by counties but by smaller units than counties like census tracts or census block groups areas, as the distribution by counties is very dissimilar. Only one-tenth of the cohort represented the non-metropolitan resident status while the rest of the cohort belonged to metropolitan resident status. Although we did find in our study that there is no significant relationship between metropolitan resident status and survival from oral tongue cancer contrary to the previous studies, we need to do further research to explore more about the effects of metropolitan residential status on cancer survival.