9-24-2020

Epidemiology, outcome, and prognostic factors of oropharyngeal lymphoepithelial carcinoma: A population-based analysis using the SEER database

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A Thesis Submitted to the Graduate Committee
of the Department of Endodontics
University of the Pacific
Arthur A. Dugoni School of Dentistry

In Partial Fulfillment of the Requirements for the Degree
Master of Science in Dentistry (Endodontics)

San Francisco
2020

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Abstract

Introduction: Lymphoepithelial carcinoma (LEC) in the oropharynx is rare. Current understanding of the disease is derived mainly from case reports and small case series, prompting further elucidation of its epidemiology and prognostic factors that affect outcome. The aim of this retrospective cohort study was to examine demographic characteristics, clinicopathologic features, and prognostic factors in patients with oropharyngeal LEC. **Methods:** The U.S. National Cancer Institute's SEER registry was queried to obtain data on patients with primary oropharyngeal LEC from 1975 to 2016. Variables examined include age at diagnosis, sex, race, year of diagnosis, primary site of tumor origin, tumor size, extent, nodal status, overall stage, tumor grade, surgical treatment, and county socioeconomic status (SES). Kaplan-Meier univariable and Cox regression model multivariable analyses were conducted to identify independent predictors of survival. **Results:** In total, 199 cases of primary LEC in the oropharynx were found. Overall survival rates at 2-, 5-, and 10-years were 81.0%, 74.0%, and 56.0%, respectively. Disease-specific survival rates at 2-, 5-, and 10-years were 85.0%, 80.0%, and 77.0%, respectively. Multivariable analysis identified older age at diagnosis, Black race, and tonsil primary site to be independent predictors of worse survival. Contrarily, a more recent year of diagnosis, surgical resection, and higher county SES were identified to be associated with an improved prognosis. **Conclusion:** Oropharyngeal LEC is a rare malignancy that is diagnosed mostly in White males in the fifth decade of life. Patient age, race, year of diagnosis, primary site of tumor origin, surgical treatment, and county SES were found to significantly affect survival. Although oropharyngeal LEC is associated with a relatively favorable prognosis,

detecting disease early and including surgical resection in treatment may aid in further improving survival.

Key words

Lymphoepithelial carcinoma; lymphoepithelioma-like carcinoma; oropharynx; Surveillance, Epidemiology, and End Results (SEER) database; outcomes

Introduction

Lymphoepithelial carcinoma (LEC), also known as lymphoepithelioma-like carcinoma, malignant lymphoepithelial lesion, or undifferentiated carcinoma, is a rare malignancy defined by the World Health Organization as "a poorly differentiated squamous cell carcinoma or undifferentiated carcinoma, accompanied by a prominent reactive lymphoplasmacytic infiltrate (1)." LEC was first used by Hilderman et al. in 1962 to describe a benign lymphoepithelial lesion with malignant features found in the parotid gland of a 40-year-old male (2).

LEC primarily manifests in the nasopharynx (3). Non-nasopharyngeal LEC in the head and neck is most commonly found in the oropharynx and major salivary glands (4–7). It can also occur in other areas throughout the body including the larynx, thymus, esophagus, stomach, lung, breast, bladder, and uterine cervix, and skin (3,8–15). Both nasopharyngeal and non-nasopharyngeal LEC are similar in histological presentation, and are distinguished by their associations with the Epstein-Barr virus (EBV) (4,16–21).

Nasopharyngeal LEC has been found to be strongly associated with EBV infection across cases regardless of the patient's race (16,17). This association has also been shown to exist in non-nasopharyngeal LEC, but mostly in patients of Eskimo/Inuit and Asian descent (22–27) and not as frequently in Caucasians (4,18–21,27). Moreover, in LEC cases of the oropharynx, hypopharynx, larynx, and uterine cervix, an association with human papillomavirus (HPV) has been reported to exist (4,14,18,28). HPV-related oropharyngeal LEC has been characterized as a less-aggressive subtype that arises more frequently in non-smoking males under 60 years old, does not metastasize to distant sites, and is highly curable with treatment (4).

In LEC of the oropharynx, over 90% occurs in the tonsils and base of tongue (1,21,28,29). Metastatic spread to regional cervical lymph nodes is common and occurs in approximately 70% of cases (1,21,30). Despite the high rate of nodal involvement, the tumor is associated with a favorable prognosis in part due to its radiosensitive attributes (1,21,29–31). It has been suggested that the lymphocytic infiltrate imparts a dilution effect that decreases the tumor's density, enabling it to respond well to radiation therapy (21). In salivary gland LEC, a good prognosis was found to also be related to a strong immune response from the presence of lymphocytic infiltration, lack of p53 and c-erb B-2 oncoproteins, and expression of bcl-2 protein (32).

Given that non-nasopharyngeal LEC is found commonly in the oropharynx, and literature regarding oropharyngeal LEC is limited to mainly case reports or small case series, the purpose of this study was to retrospectively assess oropharyngeal LEC in a larger population using data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry. Demographic characteristics, clinicopathologic features, and prognostic factors were examined and used to determine overall survival (OS) and disease-specific survival (DSS). County-level socioeconomic factors were also evaluated.

Methods

In this retrospective cohort study, data pertaining to patients diagnosed with LEC in the oropharynx was collected from the U.S. National Cancer Institute's SEER registry (www.seer.cancer.gov). The SEER database covers 27.8% of the U.S. population and represents 19 U.S. geographical regions. Informed consent and institutional review board approval were

not required for this study as the health information provided by the SEER database are de-identified and publicly available. Investigators in a previous study have validated the use of the SEER database for the analysis of LEC (6).

All cases of primary oropharyngeal LEC were selected in the database from 1975-2016. The following sites and site codes from the *International Classification of Diseases for Oncology, Third Edition* (33) were used: base of tongue (C01.9 and C02.4), soft palate (C05.1-C05.2), tonsil (C09.0-C09.1 and C09.8-C09.9), and other oropharyngeal sites/oropharynx not otherwise specified (NOS) (C10.0-C10.4 and C10.8-10.9). Only first cancers with a histologic subtype of lymphoepithelial carcinoma (code 8082) were included. Data collected using SEER*Stat 8.3.6 software included age at diagnosis, sex, race, year of diagnosis, primary site of tumor origin, tumor size, extent, nodal status, overall stage, tumor grade, surgical treatment, county socioeconomic variables (SES), survival time in months, and vital status. Radiotherapy and chemotherapy data were also collected, but not statistically evaluated due to limitations associated with its analysis, including incompleteness of the variables and potential treatment decision biases.

Race was categorized as White, Black, and other, which include Asians, Pacific Islanders, and Native Americans. Primary sites of tumor origin comprised of base of tongue, palatine tonsils, and other, which include soft palate, vallecula, posterior wall of oropharynx, branchial cleft, overlapping lesion of oropharynx, and oropharynx, NOS. Tumor grade was classified as low (well or moderately differentiated) or high (poorly differentiated or undifferentiated).

SES variables were collected from the patient's county of residence and included median family income, percentage of individuals 25 years or older with less than a high school

education, percentage of people below the federal poverty level, and percentage of unemployed people 16 years or older. Each SES variable was categorized into quartiles where the lowest quartile represented lower income, less education, more poverty, and more unemployment. All four SES variables were weighted equally and aggregated to generate a composite SES score. The lowest quartile of the composite SES score was evaluated against the rest of the cohort. This method for assessing SES variables has been performed and validated in previous studies (34–36).

All statistical analyses were performed using SPSS Statistics version 21 software (IBM). Primary outcomes were overall survival (OS), defined as time from diagnosis to death from any cause, and disease-specific survival (DSS), defined as time from diagnosis to death related to the malignancy. Median survival time was determined in years at which one-half of the patients were still alive. OS and DSS curves were produced using Kaplan-Meier analysis and effects of each variable on survival rates were assessed using the log-rank test. Covariates significantly associated with survival in univariable analysis were chosen for multivariable Cox regression survival analysis. The proportional hazards assumption was evaluated for each variable by using an interaction term between the variable and time, and assessing the significance of the interaction term. Cases with variables that had missing or unknown data were excluded from analysis. Findings were considered to be statistically significant when $p<0.05$.

Results

The SEER database query returned 199 cases of primary LEC in the oropharynx between 1975 and 2016. The patient age at diagnosis ranged from 30 to 90 years, with a median and

mean age of 56 and 56.9 years, respectively (Table 1). A majority of patients were male (72.4%). Of race, 85.4% of patients were White, 8.1% of patients were Black, and 6.6% were other (Asians, Pacific Islanders, and Native Americans). Among the patients, 8.5% were diagnosed in the 1970s, 7.0% in the 1980s, 11.1% in the 1990s, 50.8% in the 2000s, and 22.6% in the 2010s. Of the tumors, 25.6% of cases were located in the base of tongue, 63.3% in the tonsillar region, and 11.1% in other areas of the oropharynx. A tumor size of less than 2 centimeters at presentation was found in 30.2% of patients, between 2 to 4 cm in 54.3%, and greater than 4 cm in 15.5%. A majority of cases at presentation had localized extent (61.7%), while 33.1% had regional extent and 5.2% had distant extent. Most cases presented with a positive nodal status (84.7%). At diagnosis, 9.5% were in stage I or II and 90.5% of cases were in stage III or IV. Of tumor grade, a majority of cases presented with high grade (98.0%), while 2.0% had low grade. Surgical treatment was performed in 54.6% of patients and not performed in 45.4%. Of the 88 patients that did not undergo surgery, 24 (27.3%) were recommended to receive surgical treatment.

OS and DSS curves produced using Kaplan-Meier analysis (Figures 1A and 1B) revealed a 2-year OS and DSS rate of 81.0% and 85.0%, respectively; 5-year OS and DSS rate of 74.0% and 80.0%, respectively; and 10-year OS and DSS rate of 56.0% and 77.0%, respectively (Table 2). Median survival time was found to be 15.1 years and 34.0 years for OS and DSS, respectively (Table 3).

Univariable analysis using the Kaplan Meier method found age at diagnosis to be statistically significant for OS (log-rank $P < 0.001$) and DSS (log-rank $P = 0.003$) (Figures 2A and 2B, Table 4), with patients age 70 and older having a poorer prognosis and a shorter median

survival time of 7.0 years and 9.3 years for OS and DSS, respectively. Sex was found to correlate with OS (log-rank *P* = 0.036) and DSS (log-rank *P* = 0.020) (Figures 2C and 2D, Table 4), with females demonstrating lower survival (OS, 10.5 years; DSS, 16.5 years). Race was also found to be statistically significant for OS (log-rank *P* < 0.001) and DSS (log-rank *P* < 0.001) (Figures 2E and 2F, Table 4), with a dismal prognosis revealed in the Black population (OS, 1.8 years; DSS, 1.9 years). Furthermore, year of diagnosis was found to significantly affect OS (log-rank *P* < 0.001) and DSS (log-rank *P* < 0.001) (Table 4), with more recent diagnoses associated with better outcome. Primary site was also found to be statistically significant for OS (log-rank *P* = 0.002) and DSS (log-rank *P* = 0.006) (Figures 2G and 2H, Table 4). Surgical treatment correlated with increased survival for both OS (log-rank *P* = 0.002) and DSS (log-rank *P* < 0.001) (Figures 2I and 2J, Table 4), and a lower SES composite score was found to be correlated with a lower prognosis for DSS (log-rank *P* = 0.008), but not OS (log-rank *P* = 0.113) (Figures 2K and 2L, Table 4).

Multivariable analysis using the Cox proportional hazards model identified patient age at diagnosis to be an independent predictor for OS, specifically age 60 to 69 (HR, 2.72; 95% CI, 1.45 to 5.14; *P* = 0.002) and age 70 and older (HR, 3.89; 95% CI, 1.84 to 8.22; *P* < 0.001). Race was also found to be statistically significant for OS, with Black patients having a worse prognosis (HR, 4.96; 95% CI, 2.51 to 9.80; *P* < 0.001). In addition, year of diagnosis (HR, 0.97; 95% CI, 0.95 to 1.00; *P* = 0.037) and higher SES (HR, 0.54; 95% CI, 0.33 to 0.86; *P* = 0.010) were revealed to be independent predictors of improved OS.

A multivariable analysis of independent determinants of DSS identified patient age 70 and older (HR, 3.43; 95% CI, 1.30-9.07; *P* = 0.013), to be significant. Black race (HR, 5.33; 95% CI,

2.24-12.71; *P* < 0.001), tonsil primary site (HR, 3.07; 95% CI, 1.10-8.56; *P* = 0.032), surgical resection (HR, 0.26; 95% CI, 0.09 to 0.75; *P* = 0.013), and greater SES (HR, 0.46; 95% CI, 0.24-0.88; *P* = 0.019) were also found to be independent predictors of DSS.

Discussion

LEC is an uncommon malignant neoplasm that usually presents in the nasopharynx. Non-pharyngeal LEC in the head and neck is most frequently found in the salivary glands and oropharynx, with oropharyngeal LEC mostly located in the tonsils and base of tongue. A neck mass has been reported to be a common initial symptom in cases of oropharyngeal LEC (7,30). The tumor may present as an ulcerated mass or submucosal swelling in the tongue, and may cause oral pain (7,30). At diagnosis, lymph node involvement is also a common finding in affected patients (4,7,28,30,31).

Due to the rarity of this disease, much of the current knowledge regarding oropharyngeal LEC is derived from case reports and small case series. Using a registry such as the SEER database allows extraction of large population-based data to gather demographic data and outcomes from a high-powered statistical study on rare tumors that are otherwise typically understood from relatively small sample size studies. In addition to larger sample sizes, such population-based studies also carry the benefit of analyzing cases from multiple geographic regions in the U.S. and of diverse SES. Studies relying on registry-based databases, however, carry limitations. These apply to the present study and include inadequate data regarding patient social habits such as smoking and alcohol use, discernment of primary treatment modality, as well as details regarding extent of surgical resection, radiation, chemotherapy,

tumor recurrence, and patient comorbidities. To our knowledge, this study is the largest analysis of the epidemiologic, outcome, and prognostic factors in patients with oropharyngeal LEC.

In the present study, we characterized the demographic characteristics and clinicopathologic features of patients with primary LEC in the oropharynx between 1975 and 2016. Multiple prognostic factors correlated with oropharyngeal LEC outcome were identified. Multivariable cox regression analysis showed that patients of older age, Black race, and lower SES were associated with a worse survival for both OS and DSS. Conversely, a more recent year of diagnosis was correlated with better OS, and surgical treatment was correlated with better DSS. Additionally, LEC in the tonsillar area was found to be significantly associated with a worse DSS compared to LEC in the base of tongue or other oropharyngeal areas.

Most affected patients were under 60 years (62.8%), with peak incidence occurring in the fifth decade of life (median: 56 years, mean: 56.9 years). This trend is concordant with previous reports for oropharyngeal LEC (4,28,29,31). This contrasts with that of salivary gland LEC, which has been reported to occur at a younger median age of ~40 (26,37). In this study, age at diagnosis was found to be a prognostic factor for outcome in both univariable and multivariable analyses, with increased age being negatively associated with survival. This relationship has also been demonstrated in literature for that of non-pharyngeal head and neck LEC (6,38). Accordingly, screening patients early for indications of oropharyngeal LEC by clinicians is thus crucial.

Cases were found to occur predominantly in White men (male to female ratio of 2.6:1), which is consistent with studies evaluating non-nasopharyngeal head and neck LEC (4,6,21,28).

Considering the association between HPV and oropharyngeal LEC (4,28), the observed increased LEC frequency in males may potentially be attributable to their higher oral HPV infection rate, which is reportedly approximately three-fold greater compared to women (39).

In comparison to the White population, Black individuals were found to have decreased survival in both Kaplan-Meier and Cox regression analyses. This finding agrees with that found by Chan et al. for non-nasopharyngeal head and neck LEC, where the non-White population was significantly associated with worse DSS (6). Again, considering HPV's association with oropharyngeal LEC, this racial disparity may potentially be related to differences in viral status. A previous study that investigated the presence of HPV between Black and White individuals with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) found that p16-positive tumors occurred more frequently in Whites than Blacks (40). Furthermore, in another study that assessed survival among Black patients afflicted with OPSCC, it was found that those negative for HPV had a lower survival outcome than those positive for HPV (41). It may not all be attributed to viral status, however, as it was found in the same study that HPV-negative Black individuals also had a decreased outcome compared to White individuals with or without HPV (41).

Comparing tumor primary sites, LEC was found to occur more frequently in the palatine tonsil followed by the base of tongue. This distribution pattern conforms to findings in literature (4,7,28,30), and may be due to the localization of lymphoid tissue at the Waldeyer's ring (21,31). Our study found tonsillar LEC to correlate with a decreased DSS compared to LEC in base of tongue in both Kaplan-Meier and Cox regression analyses. This poorer outcome seemingly contradicts the higher median survival time for tonsillar LEC reported in Table 3,

which may be explained by examining the Kaplan-Meier DSS plot for primary site (Figure 2H). Upon closer inspection, the longest follow-up for base of tongue LEC occurred at 238 months, whereas the longest follow-up for tonsillar LEC was 419 months. The shorter follow-up time likely contributed to a lower median survival time for base of tongue LEC. Survival curves for base of tongue LEC actually appear to indicate a better prognosis compared to that of tonsillar LEC, which is supported by the increased tonsil primary site HR shown in Table 5. Since base of tongue LEC patients appear to have a higher survival rate, it may be conceivable that these patients ceased follow-ups after a certain period, as opposed to patients with tonsillar LEC.

Treatment for non-nasopharyngeal LEC consists of primary radiotherapy or surgery, or a combination of radiotherapy, surgery, and/or chemotherapy (21). Because non-nasopharyngeal LEC is a radiosensitive disease (30,31), radiotherapy is considered to be an appropriate first-line treatment, especially for locoregionally advanced disease (7). Surgery is usually recommended if persistent disease exists after radiotherapy has been completed (7). This may involve removal of affected lymph nodes through neck dissection, and modified to radical neck dissection depending on the level of nodes involved (5,29). Previous studies have demonstrated the effectiveness of these treatments. Klijanienko et al. found high radiocurability of localized tonsillar LEC and reported a 10-year overall survival rate of 77% (31). Moreover, Singhi et al. showed that all 21 oropharyngeal LEC patients who underwent some combination of radiotherapy, surgery, and chemotherapy had no tumor recurrence or death due to disease (4). Bansberg et al. found that a combined therapy of surgical excision followed by radiation improved prognosis (30). Our analysis supports these findings and demonstrated surgical excision to be associated with significantly improved DSS in both univariable and multivariable

analyses. We stratified the surgery variable into three groups: 1) surgery recommended, but not performed, 2) surgery not recommended and not performed, 2) surgery performed. Interestingly, the second group did not show a significantly improved prognosis compared to the first group (Table 5) and median DSS times were similar between the two groups (Table 3), further suggesting that surgical resection combined with radiotherapy may be beneficial in prolonging survival.

In regard to other treatment types, 85.9% of patients underwent radiotherapy while the rest were classified as "none/unknown." Chemotherapy occurred in 51.8% of patients while the other 48.2% were "none/unknown." Because it is not possible to distinguish between patients who did not receive treatment versus those that are unknown, the radiation and chemotherapy treatment variables were deemed inadequate for comparing outcomes and were excluded from statistical analysis. However, in patients who definitively received treatment, we were able to assess how the addition of surgical resection affected outcome. Of the 171 patients who received radiotherapy, 91 (53.2%) also underwent surgery; 12 (13.2%) of those patients suffered disease-specific death. In 18 patients (10.5%) who did not undergo surgery when it was recommended, 6 (33.3%) died a disease-specific death. In 58 patients (33.9%) who were not recommended surgery, 15 (25.9%) died of disease. These results suggest that even with radiotherapy, the addition of surgery appears to be valuable in improving prognosis.

While the SEER database does not provide patient-level SES data, available county-level SES data may provide clues regarding a patient's access to health care. County-level SES was found to be a significant prognostic factor for survival in both Kaplan-Meier univariable and Cox regression model multivariable analyses. An association was found between those living in

counties of residence with the lowest composite SES score and decreased OS and DSS. Counties that are the poorest and least educated may lack adequate resources and present barriers to care for its residents. Consequently, individuals residing in these counties may have limited access to medical care, likely resulting in a delay in disease diagnosis and treatment, and a decreased survival rate.

Tumor extent, size, and nodal status were not found to be significant prognostic factors for outcome in our univariable analysis and were thus excluded from multivariable analysis. Concerning nodal status, a majority of patients presented with lymph node involvement (84.7%), an incidence within the range that has been reported in literature (72.2%-86%) (4,7,28,30,31). Despite a high rate of positive nodal status, studies have shown that excellent disease control is achievable in these patients (4,31). However, patients with lymph node involvement are also at higher risk for distant metastasis and treatment failure (7,30).

Data on tumor stage was collected, but not included in the statistical analysis as many data points were missing. Of those recorded, nearly all were in an advanced clinical stage, as previous studies have also found (4,30). Likewise for tumor grade, the variable was not useful for analysis as nearly all cases had a high grade, and therefore excluded from statistical analysis.

While EBV has been reported to be strongly linked to non-nasopharyngeal LEC patients of Eskimo/Inuit and Asian descent (22–27), the association is less consistent in White individuals (4,18–21,27). Alternatively, an association between oropharyngeal LEC and HPV has been reported to exist (4,28). The SEER database does not provide information regarding patient EBV or HPV status. Therefore, an association with either virus in oropharyngeal LEC patients was not ascertained in this study.

In conclusion, oropharyngeal LEC is a rare malignant tumor that is diagnosed mostly in White males in the fifth decade of life. A majority of cases are located in the palatine tonsils and present in a clinically advanced stage with lymph node involvement. Even in such progressive cases, the prognosis remains relatively favorable. Oropharyngeal LEC was found to be associated with a 5-year OS of 74.0% and 5-year DSS of 80.0%. Nevertheless, detecting disease early and including surgical resection in treatment may aid in further improving prognosis.

TABLE 1: Patient demographic, tumor, and treatment characteristics of 199 cases of oropharyngeal lymphoepithelial carcinoma in the Surveillance, Epidemiology, and End Results database (1975-2016)		
CHARACTERISTIC	**No. of patients**	**Percentage of patients†**
Age, y		
<50	47	23.6
50-59	78	39.2
60-69	49	24.6
≥70	25	12.6
Sex		
Male	144	72.4
Female	55	27.6
Race		
White	169	85.4
Black	16	8.1
Other	13	6.6
Unknown	1	
Year of diagnosis		
1975-1979	17	8.5
1980-1989	14	7.0
1990-1999	22	11.1
2000-2009	101	50.8
2010-2016	45	22.6
Primary site		
Base of tongue	51	25.6
Tonsil	126	63.3
Other*	22	11.1
Tumor size, centimeters		
<2	35	30.2
2-4	63	54.3
>4	18	15.5
Unknown	83	
Extent		
Localized	95	61.7
Regional	51	33.1
Distant	8	5.2
Unknown	45	
Nodal status		
Negative	25	15.3
Positive	138	84.7
Unknown	36	
Overall stage		
I or II	4	9.5
III or IV	38	90.5
Unknown	157	
Tumor grade		
Low (well or moderately differentiated)	3	2.0
High (poorly differentiated or undifferentiated)	145	98.0
Unknown	51	
Surgery		
No (recommended)	24	12.4
No (not recommended)	64	33.0
Yes	106	54.6
Unknown	5	
Radiation therapy		
None/unknown	28	14.1
Yes	171	85.9
Chemotherapy		
None/unknown	96	48.2
Yes	103	51.8
* Races in "Other" group include Asians, Pacific Islanders, and Native Americans.		
† Percentages may not add up to 100% due to rounding.		

TABLE 2: Percentage survival according to year		
YEAR	**OVERALL SURVIVAL**	**DISEASE-SPECIFIC SURVIVAL**
2	81.0	85.0
5	74.0	80.0
10	56.0	77.0

TABLE 3: Median survival time in years		
CHARACTERISTIC	**OVERALL SURVIVAL**	**DISEASE-SPECIFIC SURVIVAL**
Median survival	15.1	34.0
Age, y		
<50	16.7	24.5
50-59	20.5	23.0
60-69	10.0	23.0
≥70	7.0	9.3
Sex		
Male	17.1	30.0
Female	10.5	16.5
Race		
White	15.9	34.1
Black	1.8	1.9
Other	18.2	18.0
Primary site		
Base of tongue	13.7	19.0
Tonsil	15.7	24.7
Other	3.5	21.0
Surgery		
No (recommended)	3.0	21.0
No (not recommended)	18.0	20.0
Yes	16.2	34.3
Composite SES score		
Lowest quartile	12.6	15.7
All others	15.6	34.1

TABLE 4: Univariable analysis of variables		
CHARACTERISTIC	**OVERALL SURVIVAL***	**DISEASE-SPECIFIC SURVIVAL***
Age	<0.001	0.003
Sex	0.036	0.020
Race	<0.001	<0.001
Year of diagnosis	<0.001	<0.001
Primary site	0.002	0.006
Tumor size	0.371	0.300
Extent	0.477	0.187
Nodal status	0.738	0.683
Surgery	0.002	<0.001
Composite SES score	0.113	0.008
* Log-rank P value.		

TABLE 5: Cox proportional hazards model for multivariable analysis						
CHARACTERISTIC	**OVERALL SURVIVAL**			**DISEASE-SPECIFIC SURVIVAL**		
	Hazard Ratio	**95% CI**	**P Value**	**Hazard Ratio**	**95% CI**	**P Value**
Age, y						
<50	Reference			Reference		
50-59	1.05	0.55-2.02	0.877	0.66	0.28-1.55	0.339
60-69	2.72	1.45-5.14	0.002	1.02	0.40-2.59	0.968
≥70	3.89	1.84-8.22	<0.001	3.43	1.30-9.07	0.013
Sex						
Male	Reference			Reference		
Female	1.24	0.76-2.03	0.392	1.57	0.78-3.13	0.203
Race						
White	Reference			Reference		
Black	4.96	2.51-9.80	<0.001	5.33	2.24-12.71	<0.001
Other	0.98	0.37-2.55	0.964	0.97	0.23-4.17	0.966
Year of diagnosis	0.97	0.95-1.00	0.037	1.00	0.96-1.03	0.834
Primary site						
Base of tongue	Reference			Reference		
Tonsil	1.13	0.63-2.05	0.678	3.07	1.10-8.56	0.032
Other	1.30	0.62-2.71	0.487	2.05	0.62-6.81	0.240
Surgery						
No (recommended)	Reference			Reference		
No (not recommended)	1.12	0.55-2.31	0.753	0.78	0.28-2.16	0.630
Yes	0.72	0.36-1.43	0.343	0.26	0.09-0.75	0.013
Composite SES score						
Lowest quartile	Reference			Reference		
All others	0.54	0.33-0.86	0.010	0.46	0.24-0.88	0.019

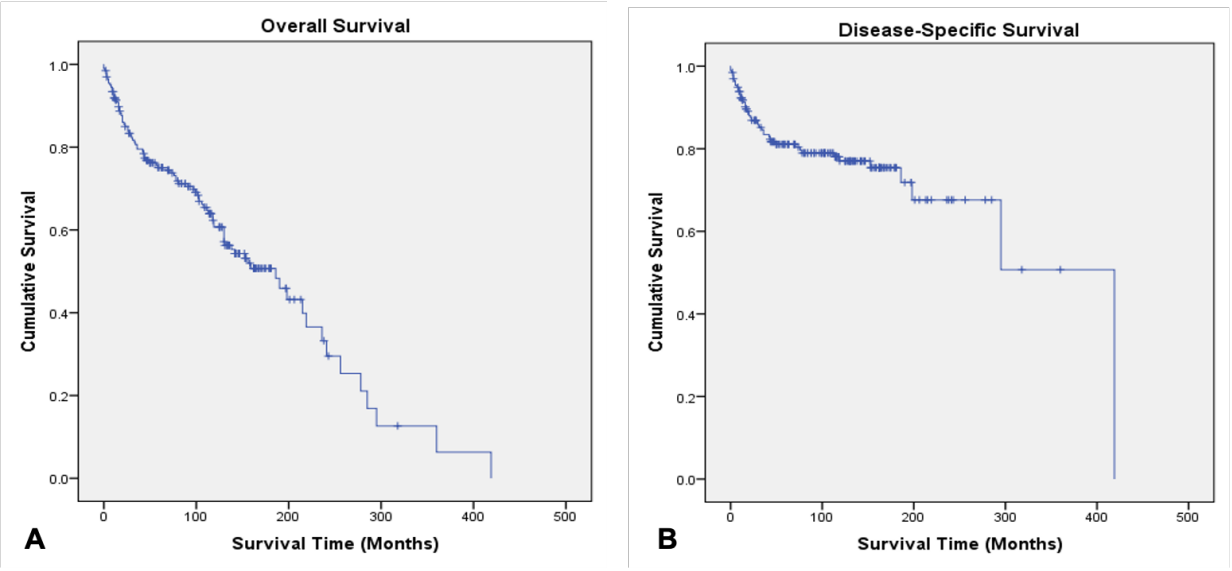
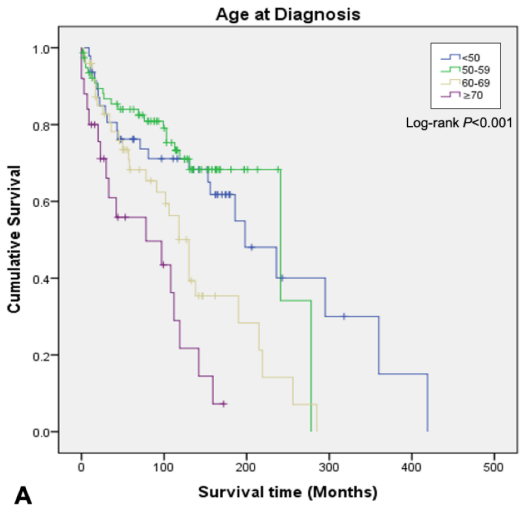
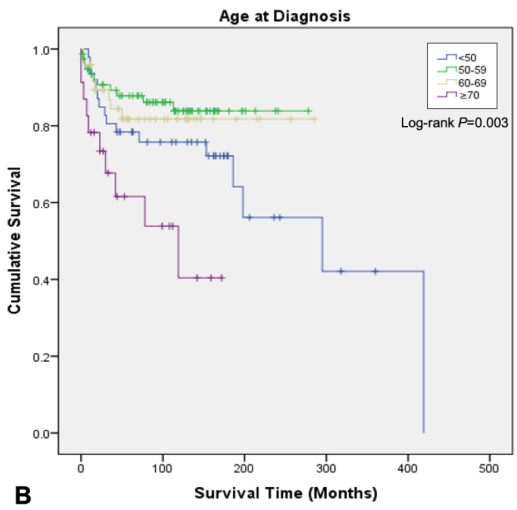


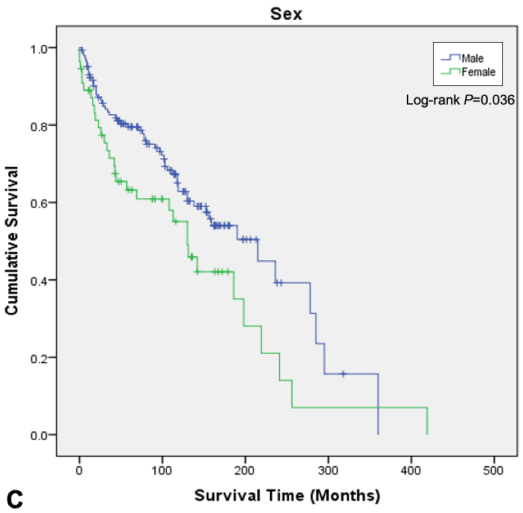
Figure 1. A. Kaplan-Meier estimates of overall survival for the entire cohort of patients. **B.** Kaplan-Meier estimates of disease-specific survival for the entire cohort of patients.


Age at Diagnosis
<50
50-59
60-69
≥70
Log-rank P<0.001
Cumulative Survival
Survival time (Months)

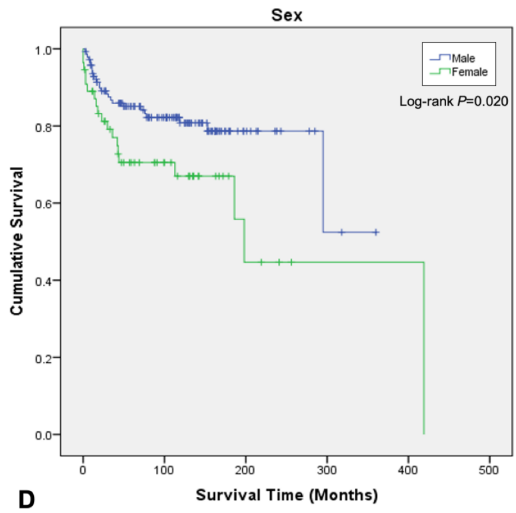
A


Age at Diagnosis
<50
50-59
60-69
≥70
Log-rank P=0.003
Cumulative Survival
Survival Time (Months)

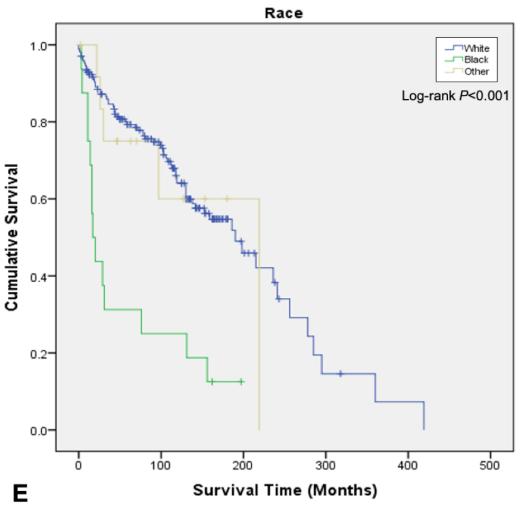
B


Sex
Male
Female
Log-rank P=0.036
Cumulative Survival
Survival Time (Months)

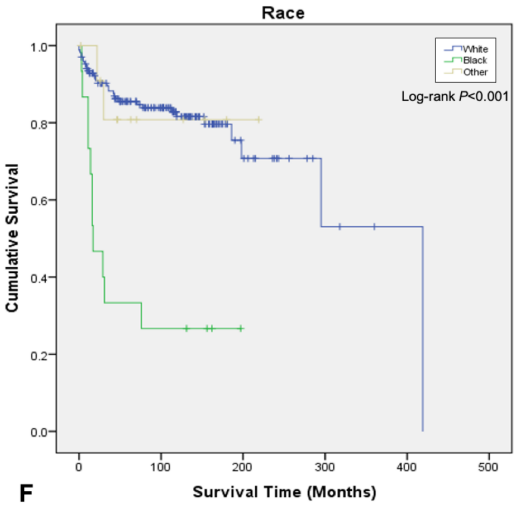
C


Sex
Male
Female
Log-rank P=0.020
Cumulative Survival
Survival Time (Months)

D


Race
White
Black
Other
Log-rank P<0.001
Cumulative Survival
Survival Time (Months)

E


Race
White
Black
Other
Log-rank P<0.001
Cumulative Survival
Survival Time (Months)

F

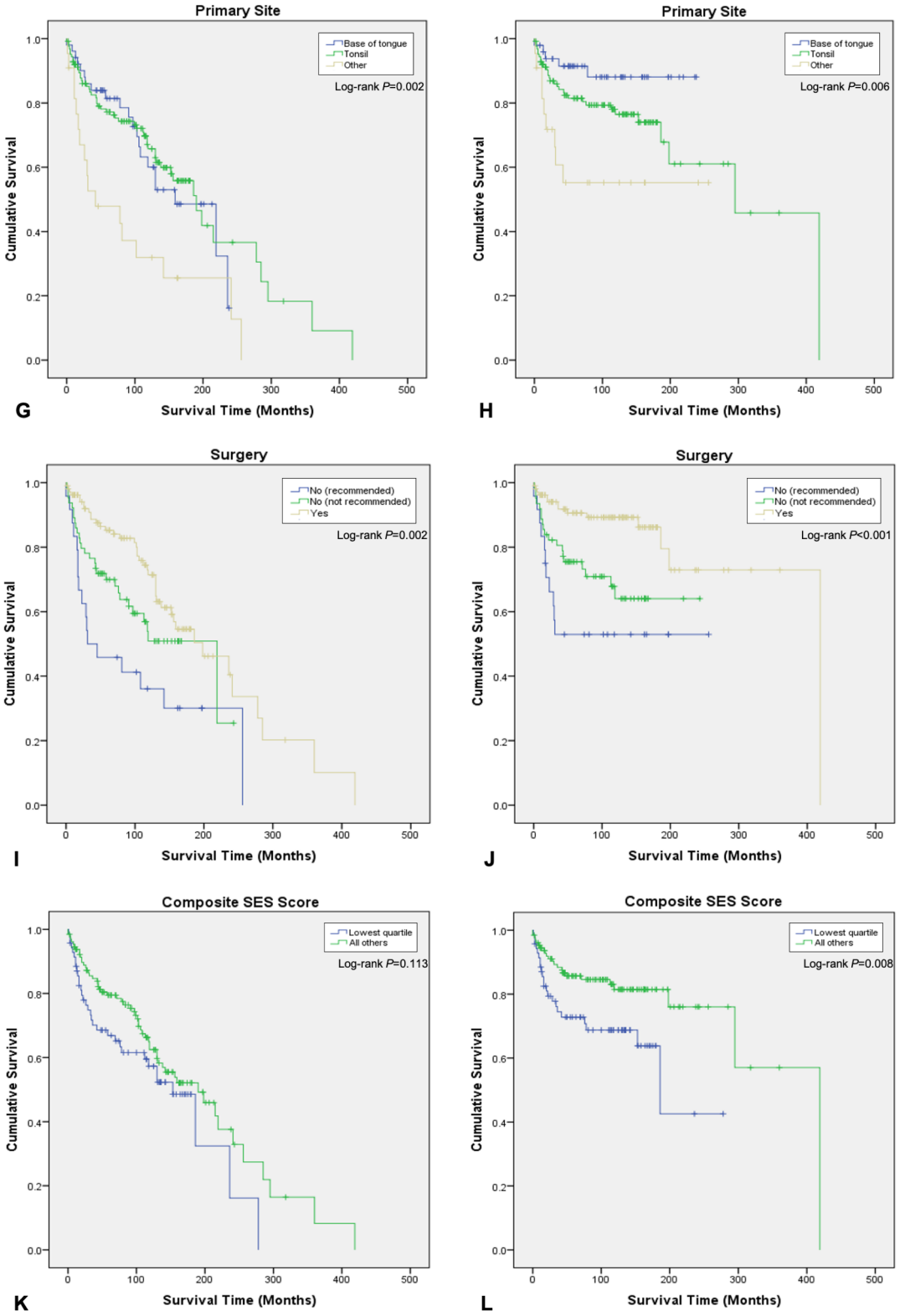


Figure 2. A. Kaplan-Meier estimates of overall survival (OS) stratified by age at diagnosis. **B.** Kaplan-Meier estimates of disease-specific survival (DSS) stratified by age at diagnosis. **C.** Kaplan-Meier estimates of OS stratified by sex. **D.** Kaplan-Meier estimates of DSS stratified by sex. **E.** Kaplan-Meier estimates of OS stratified by race. **F.** Kaplan-Meier estimates of DSS stratified by race. **G.** Kaplan-Meier estimates of OS stratified by primary site. **H.** Kaplan-Meier estimates of DSS stratified by primary site. **I.** Kaplan-Meier estimates of OS stratified by surgery performed. **J.** Kaplan-Meier estimates of DSS stratified by surgery performed. **K.** Kaplan-Meier estimates of OS stratified by composite socioeconomic status (SES) score. **L.** Kaplan-Meier estimates of DSS stratified by composite SES score.

Acknowledgements

The authors would like to gratefully thank Gloria C. Chi, PhD, and Eric S. Salmon, DDS, MS, for reviewing our statistical analysis and providing useful comments.

Compliance with Ethical Standards

Funding source: None.

Conflict of interest: None.

Informed consent: None required.

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