



# Clinicopathological characteristics and prognostic analysis of lymphoepithelial carcinoma of salivary gland: a population-based study

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**Background:** The purpose of this study was to elucidate the clinicopathological characteristics of patients with lymphoepithelial carcinoma of salivary gland (LEC-SG) and determine the factors associated with survival.

**Methods:** A total of 179 LEC-SG patients from the Surveillance, Epidemiology, and End Results (SEER) database between 1975 to 2016 were included. The clinicopathological characteristics and overall survival of LEC-SG patients were described, and the features affecting prognosis were further determined using Kaplan-Meier Curves and Cox survival analysis.

**Results:** The median overall survival of LEC-SG patients was 206 months, and the 1-, 5-, 10- and 20-year survival rates were 91.0%, 80.2%, 66.4%, and 37.6%, respectively. The prognoses were significantly associated with age, ethnicity, marital status, tumor invasion, as well as lymph node metastases [ $P < 0.01$  for all]. Surgical resection could significantly improve the prognosis of this disease (median overall survival (mOS): 219 *vs.* 68 months,  $P < 0.01$ ). Postoperative radiotherapy could improve long-term survival and decrease the risk of death among patients who survive exceed 10-year after surgery. The Cox regression analysis showed that old age ( $>60$  years) and lymph node metastases were independently associated with poor survival ( $P < 0.05$  for both). Conversely, the use of surgery was an independent favorable prognostic factor [hazard ratio (HR) 0.29, 95% CI: 0.13–0.66].

**Conclusions:** LEC-SG patients had a favorable prognosis with a mOS of 206 months. Old age, lymph node metastases, the use of surgery were independently associated with survival of LEC-SG patients.

**Keywords:** Salivary gland tumor; lymphoepithelial carcinoma (LEC); Surveillance, Epidemiology, and End Results database (SEER database); prognosis

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## Introduction

Lymphoepithelial carcinoma (LEC) is a rare malignancy characterized by a poorly differentiated carcinoma accompanied by a prominent non-neoplastic lymphoplasmacytic infiltration (1). LEC was often occurred

in the nasopharynx, accounting for 40% of all nasopharynx neoplasms (2). Except for the nasopharynx, it could also occur in other site in the head and neck region and previous studies showed LEC represents approximately 5% of head and neck cancers (3,4). Epstein-Barr virus (EBV) infection

is considered to be contributing factor for the initiation and development of this disease, so LEC has a unique ethnic predilection for Eskimo, Chinese and Japanese population (5,6). In addition, LEC is also associated with tobacco and alcohol use (7). Similar to other pathological type, the combination of surgery and postoperative radiotherapy is the mainstay treatment paradigm for LEC patients (8). Due to significant lymphocytic infiltration in LEC tissue which could induce a strong anti-tumor immune response, the previous studies reported that LEC patients often had good prognosis (8,9).

LEC of salivary gland (LEC-SG) is exceedingly rare and only comprises 0.4% of salivary malignancies (10). Due to its rarity, most knowledge and information about this disease comes from case report or case series. The clinicopathological characteristics and prognosis of LEC-SG patients has not fully defined. To better understand this rare malignancy, we conducted a population-based study to present the clinicopathological characteristics, and further determine the prognostic factors using the data of LEC-SG patients registered in Surveillance, Epidemiology, and End Results (SEER) database between 1975 to 2016. We present the following article in accordance with the STROBES reporting checklist (available at <http://dx.doi.org/10.21037/ggs-20-464>).

## Methods

### *Data source and participants*

The database 'SEER 18 Regs Custom Data with additional treatment fields, Nov 2018 Sub (1975-2016)' was searched. We accessed the SEER database with the dedicated software SEER\*Stat (<http://seer.cancer.gov/seerstat>) and obtained all available cases of primary LEC located in salivary glands, with ICD-O-3 histology coding (ICD-O-3:8310/3) between 1975 and 2016. In each case, age at diagnosis, sex, ethnicity, TNM-AJCC stage, SEER historic stage, the use of radiotherapy/chemotherapy/surgery were recorded. The overall survival time was also isolated from the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Statistical analysis*

The clinicopathological characteristics were summarized using counts and percentages. Student's *t*-tests and chi-square tests were used to evaluate the difference in

continuous data and categorical data, respectively. The Kaplan-Meier Curves were drawn, survival analysis was assessed by Log-Rank test. The association of each characteristic with prognosis was evaluated using univariate and multivariate Cox regression models. MedCalc statistical software was used for all statistical analysis (Mariakerke, Belgium). A P value less than 0.05 was considered statistically significant.

## Results

### *Clinicopathological characteristics of LEC-SG patients*

Totally, 179 patients diagnosed with LEC-SG were identified from SEER database between 1975 and 2016 (Table 1). A total of 93 out of 179 patients were female and another 86 cases were male. The average age at initial diagnosis was 60.2 years (60.2±18.2 yr). This disease was common in the parotid gland (153/179), followed by submandibular gland (23/179). The distribution of the presenting stages of LEC of salivary gland was (63/179) distant stage, (77/179) regional stage, (20/179) localized stage. As for treatment regimen, most patients (166/179) underwent surgery, 119 patients (119/179) received radiotherapy after surgery and 33 patients received chemotherapy.

### *Overall survival of LEC-SG patients*

As shown in Figure 1A, the median OS (mOS) of all 179 LEC-SG patients was 206 months (95% CI: 143–262 months), with the 1-, 5-, 10- and 20-year survival rates of 91.0%, 80.2%, 66.4%, and 37.6%, respectively. Patients with distant stage or regional stage (SEER historic stage) had relatively shorter overall survival time than those with localized stage, but no significantly statistical difference could be observed (P=0.12, Figure 1B). According to TNM-AJCC stage classification, patients with advanced stage (III/IV) had significantly shorter overall survival time than those with early stage (I/II) (P<0.05, Figure 1C).

### *Features influencing overall survival*

The stratification analysis showed that LEC-SG patients who were non-white/black ethnicity had significantly better prognosis than white/black individuals (P<0.05, Figure 2A). The prognoses of LEC-SG patients became much worse with increasing age, increasing tumor invasion and lymph

**Table 1** Clinicopathological characteristics of 179 patients with LEC of salivary gland

Characteristics	Total
Age (year)	60.2±18.2
Gender	
Female	93 (52.0%)
Male	86 (48.0%)
Ethnicity	
White	109 (60.9%)
Black	11 (6.1%)
Other (American Indian/AK Native, Asian/Pacific Islander)	59 (33.0%)
Pathological differentiation	
Poorly	56 (60.2%)
Undifferentiated	37 (39.8%)
Unknown	86
Summary stage	
Distant	20 (12.5%)
Regional	77 (48.1%)
Localized	63 (39.4%)
Unstaged	19
Primary site	
Parotid gland	153 (85.5%)
Submandibular gland	23 (12.8%)
Major salivary gland, NOS*	3 (1.7%)
Laterality	
Left	80 (45.5%)
Right	96 (54.5%)
Unknown	3
Tumor size	
T1	17 (21.3%)
T2	29 (36.2%)
T3	21 (26.3%)
T4	13 (16.2%)
Unknown	99
Lymph node metastases	
N0	42 (46.7%)
N1	47 (53.3%)
Unknown	90

**Table 1** (continued)**Table 1** (continued)

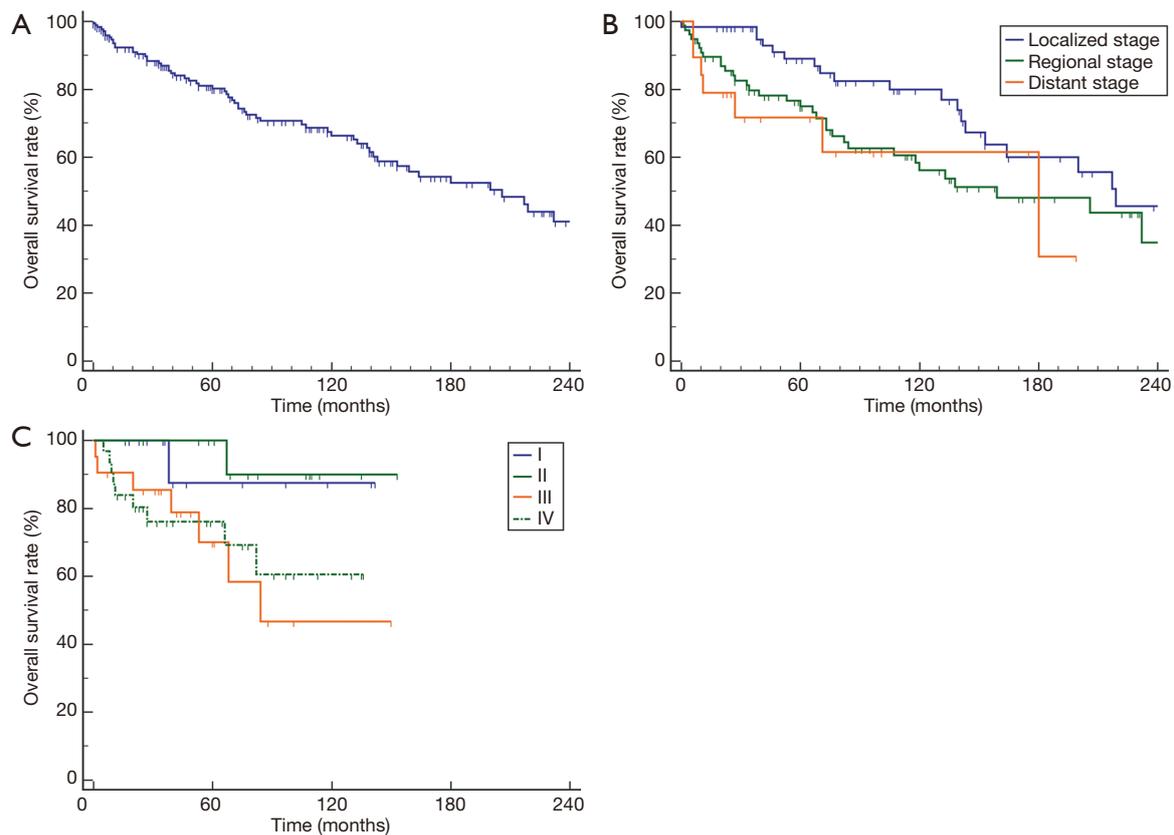
Characteristics	Total
Distant metastases	
M0	87 (97.8%)
M1	2 (2.2%)
Unknown	90
TNM stage	
I	14 (17.1%)
II	16 (19.5%)
III	21 (25.6%)
IV	31 (37.8%)
Unknown	97
Surgery	
Yes	166 (92.7%)
No	13 (7.3%)
Radiotherapy	
Yes	127 (70.9%)
No	52 (29.1%)
Chemotherapy	
Yes	33 (18.4%)
No/unknown	146 (81.6%)

\*NOS: not stated. The type of major salivary gland of these 3 patients were not stated. LEC, lymphoepithelial carcinoma; TNM, tumor-node-metastases.

node metastases ( $P<0.01$ , *Figure 2B,C,D*). Only 2 patients with distant metastases could survive more than 25 months. Divorced or widowed patient had worse prognosis than married or unmarried patients ( $P<0.01$ ). In addition, the results showed no significant association of other characteristics and prognosis including gender ( $P=0.22$ ), laterality ( $P=0.29$ ), pathological grade ( $P=0.60$ ), primary site ( $P=0.12$ ).

### ***Effect of treatment regimen on prognosis***

*Figure 3* showed the effect of different treatment regimens on prognosis. Patients received surgical resection had much longer overall survival time than those who did not received surgery (mOS: 219 vs. 68 months,  $P<0.01$ ). The use of radiotherapy could also prolong the overall survival of LEC-SG patients, but without significantly statistical difference (mOS: 231 vs. 138 months,  $P=0.11$ ; *Figure 3B*).



**Figure 1** Overall survival of patients with LEC of salivary gland: (A) overall survival of all 179 patients; (B) overall survival stratified by SEER historic stage; (C) overall survival stratified by TNM stage. LEC, lymphoepithelial carcinoma; SEER, the Surveillance, Epidemiology, and End Results Database.

Meanwhile, there was no statistically significant difference in overall survival between LEC-SG patients with and without chemotherapy ( $P=0.18$ ; *Figure 3C*). In addition, the combination of surgery and radiotherapy also could prolong the overall survival than those with surgery alone. Radiotherapy after surgery could improve long-term survival and decrease the risk of death among patients who survive exceed 10 year after surgery (232 vs. 143 months,  $P=0.25$ ; *Figure 3D*).

### Cox regression survival analyses

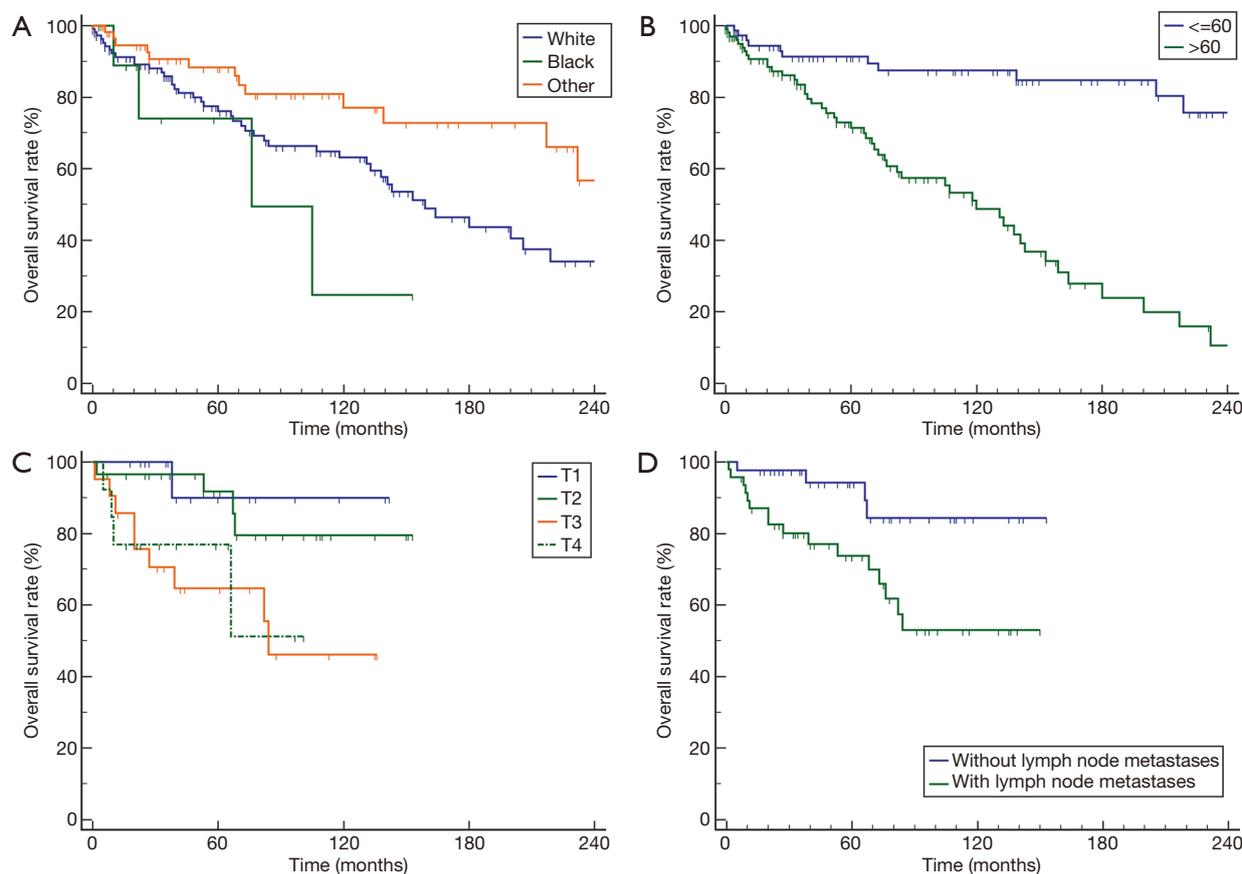
The potential features affecting survival were evaluated using univariate and multivariate Cox regression model (*Table 2*). The univariate analysis revealed that age, race, marital status, lymph node metastases as well as the use of surgery were significantly associated with overall survival. Old age, non-white/black race, divorced/widowed status,

lymph node metastases was associated with poor survival, while surgical resection was associated with good prognosis ( $P<0.05$ ). The multivariate analysis showed that old age (>60 years) as well as lymph node metastases were independent prognostic risk factors for LEC-SG patients. Conversely, the use of surgery was an independent favorable prognostic factor (HR =0.29, 95% CI: 0.13–0.66; *Table 2*).

### Discussion

The purpose of the present study was to elucidate the clinicopathological characteristics and prognosis of LEC-SG patients using the data of 179 patients from SEER database. The results showed that LEC of salivary gland had good prognosis with a mOS of 206 months, and old age, lymph node metastases as well as the use of surgery were independent prognostic factors.

LEC of salivary gland is exceedingly rare, it only

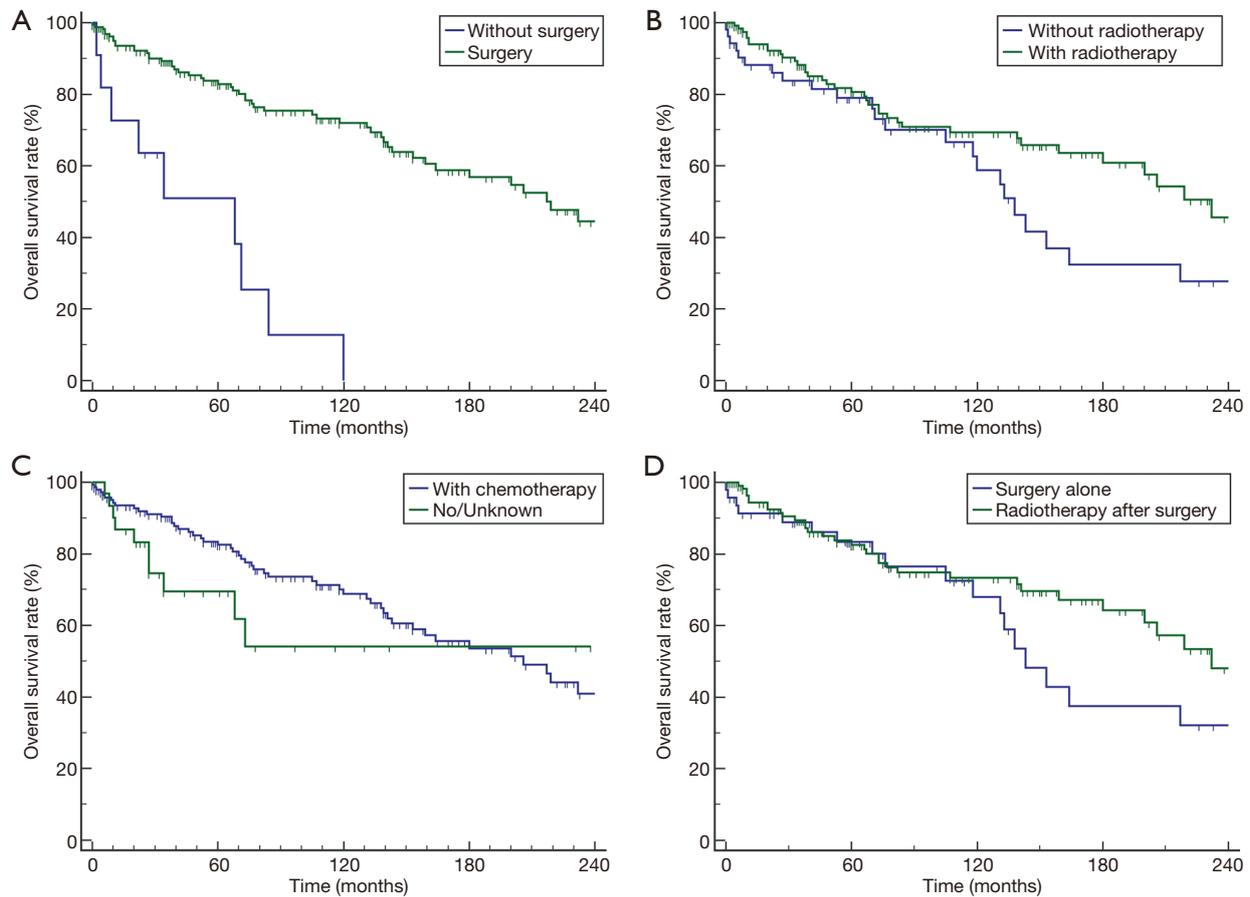


**Figure 2** Overall survival for patients with salivary gland stratified by clinicopathological characteristics: (A) race; (B) age; (C) tumor stage; (D) lymph node metastases.

comprises 0.4% of salivary malignancies in Western country. Chinese patients have a relatively higher incidence of LEC, accounting for approximately 5–9.7% of all salivary gland tumors (11,12). The present study showed that LEC of salivary gland is much more frequent in the non-white/black population than white or black population. Due to the invariable relationship between EBV and LEC, this regional difference in the occurrence of this disease may be attributed to cancer-related virus infection (1,7). For example, several previous studies have reported a close correlation of EBV infection with LEC development in Southeast Asia, Greenland, and Alaska (8,13,14). EBV positivity was also observed in LEC-SG patients from high incidence regions. For example, Ma found that EBV-DNA was positive in 43.9% (18/41) of Chinese LEC patients at initial diagnosis (8). The recent data demonstrated that 85.0% of lesions were located in parotid gland, which is in consistent with previous data (15,16). Previous studies have

some controversial results about the gender distribution of this disease. Wang YL, *et al.* reported a predominance of men with a female-to-male ratio of 1:1.75 among 11 cases with LEC of salivary gland (12). Another study including 103 cases reported this disease predominantly occurs in women, with a male-female ratio of 1:1.94 (16). Similar to Ma H's study, we also observed that 52% patients were women, with a female-to-male ratio of 1.08:1 (8). Several studies in Chinese population reported that the average age of LEC of salivary gland was around 50 years (49.4–51.8 years) (8,11,16), but the age of patients in the present cohort was older than previous studies that the LEC-SG patients had an average age of 60.2 years, with 102 cases older than 60 years.

Among LEC-SG patients, several studies have reported nonspecific symptoms could lead to a delay in a definitive diagnosis of this malignancy, with a median delay period of 12 months (7 days to 20 years) (8,11,16). Consequently, a majority of patients with LEC of salivary gland present



**Figure 3** The effect of different treatments on overall survival for patients LEC of salivary gland: (A) surgery; (B) radiotherapy; (C) chemotherapy; (D) radiotherapy after surgery. LEC, lymphoepithelial carcinoma.

locally or regionally advanced disease at diagnosis. In Ma H' study, 59.4% of patients were categorized into advanced stage (III/IV), and 43.5% of patients had lymph node metastases. In our study, the data revealed that 58.9% of patients were categorized into regional or distant stage at initial diagnosis, and 52.8% of patients had lymph node metastases. Only 2 cases in the present cohort had distant organ metastases, one case had bone metastases, the other one had no information about distant metastases.

In consistent with previous studies, the recent data also demonstrated that LEC-SG patients had a relatively better prognosis. The mOS for all LEC-SG patients was 206.0 months, with a 10-year survival rate of 66.4%. And, almost 38% of patients with LEC of salivary gland could survive exceed 20 years. The survival time of those patients is much longer than the reported data of other types of salivary gland malignancies including salivary malignant pleomorphic adenoma, mucoepidermoid carcinoma,

adenoid cystic carcinoma (8,11,16). As for treatment regimen, surgery is undoubtedly the preferred choice of treatment among patients with LEC of salivary gland. Even patients were diagnosed with stage IV, previous study reported 84.2% cases could receive neck dissection (8,11,16). Our data showed that 92.7% of all patients and 29 of 31 stage IV patients had undergone surgery. Radiotherapy was also an important treatment regimen. In the present study, 70.9% patients received radiotherapy and 66.5% patients received postoperative radiotherapy. However, the survival analysis in the present cohort demonstrated that postoperative radiotherapy could not significantly prolong survival time when compared with surgery alone, but postoperative radiotherapy could improve the long-term survival. For example, the 10-, 15-year survival rates were 71.5% and 68.0%, 64.3% and 32.1% for patients who received postoperative radiotherapy or not, respectively. One possibility is that postoperative

**Table 2** Univariate and multivariate Cox proportional hazard analyses of the characteristics for overall survival in patients with LEC of salivary gland

Factor	Category	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age	≤60	Reference		Reference	
	>60	5.80 (3.03–11.1)	<0.01	5.09 (2.58–10.04)	0.03
Gender	Female	Reference			
	Male	1.37 (0.83–2.25)	0.22		
Race	White	Reference			
	Black	1.82 (0.65–5.10)	0.36	1.45 (0.51–4.13)	0.48
	Other	0.55 (0.31–0.99)	0.04	0.74 (0.38–1.43)	0.37
Marital status	Married	Reference			
	Unmarried	2.38 (1.37–4.14)	0.55	1.58 (0.91–2.76)	0.67
	Divorced/widowed	1.28 (0.56–2.92)	<0.01	1.34 (0.34–5.23)	0.11
Pathological differentiation	Poorly	Reference			
	Undifferentiated	0.75 (0.36–1.55)	0.44		
Primary site	Parotid gland	Reference			
	Submandibular gland	1.71 (0.93–3.14)	0.08		
Laterality	Left	Reference			
	Right	1.37 (0.68–1.98)	0.23		
Summary stage	Localized	Reference			
	Regional	1.60 (0.93–2.77)	0.09		
	Distant	2.12 (0.89–5.02)	0.09		
Tumor invasion	T1	Reference			
	T2	2.03 (0.23–18.1)	0.53		
	T3	7.88 (0.99–61.6)	0.06		
	T4	7.60 (0.86–67.3)	0.07		
Lymph node metastases	N0	Reference			
	N1	3.97 (1.34–11.8)	0.01	3.44 (1.11–10.7)	0.03
Surgery	Yes/no	0.16 (0.08–0.34)	<0.01	0.29 (0.13–0.66)	<0.01
Radiotherapy	Yes/no	0.66 (0.39–1.10)	0.11		
Chemotherapy	Yes/no + unknown	1.59 (0.80–3.17)	0.18		

The COX analysis of distant metastases could not be conducted due to inadequate data. LEC, lymphoepithelial carcinoma; HR, hazard ratio; CI, confidence interval.

radiotherapy could decrease the risk of recurrence among those patients. For example, Ma H's study reported that postoperative radiotherapy was associated independently with relapse-free survival, but not overall survival (8,11,16).

Therefore, postoperative radiotherapy was recommended for the patients with high-risk indications such as R1 resection with microscopically positive margins, lymph node metastases, etc. (17). Except for surgery and radiotherapy,

chemotherapy could be also used in treatment of LEC-SG patients. In the present study, we could not observe any significant relationship of the use of chemotherapy with the overall survival among LEC-SG patients. As we known, no adequate information about the use of chemotherapy including chemotherapy regimens could be extracted from the SEER database, which limited the accuracy and reliability of the conclusion concerning the effect of chemotherapy among LEC-SG patients. For example, there are some similarities in histology between LEC and nasopharyngeal carcinoma, whether the commonly used chemotherapy regimens for nasopharyngeal carcinoma could also provide clinical benefit for LEC-SG patients still need to be further proven.

In conclusion, the results revealed that LEC-SG patients had a favorable prognosis and old age, lymph node metastases as well as the use of surgery were significantly associated with prognosis. Although there are several limitations similar to other analysis based on the SEER database including inadequate information, retrospective nature, small sample size, the present study is the largest series of cases with LEC-SG and could help the physician more deeply understand this malignancy.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/gs-20-464>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-20-464>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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