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Original Article

Lymphoepithelial carcinoma of the oral cavity and pharynx: a SEER population-based cohort study

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Abstract: Objectives: Lymphoepithelial carcinoma (LEC) of the oral cavity and pharynx is a rare cancer, with poorly understood clinicopathological characteristics and prognosis. Only a few case reports or small case series have been reported, so the characteristics and survival of patients with this disease remains unclear. The present study aimed to describe the clinicopathological characteristics and determine the factors associated with survival of this uncommon cancer. Methods: A population-based study was carried out to investigate clinical characteristics and prognosis of LEC of the oral cavity and pharynx using the data from Surveillance, Epidemiology and End Results (SEER) database. Log-Rank test and Cox regression analysis were performed to determine the prognostic factors, and a prognostic nomogram was further constructed. The propensity-matched analysis was conducted to compare the survival of nasopharyngeal LEC and non-nasopharyngeal LEC patients. Results: Totally, 1025 patients were identified, including 769 nasopharyngeal LEC patients and 256 non-nasopharyngeal LEC patients. The median OS of all patients was 232.0 months (95% CI 169.0-258.0). The 1-, 5-, 10- and 20-year survival rates were 92.9%, 72.9%, 59.3%, and 46.8%, respectively. Surgery significantly prolonedg the survival of LEC patients (P<0.01, mOS: 190 m vs. 255 m). Radiotherapy, as well as radiotherapy after surgery, prolonged the mOS (P<0.01 for both). The survival analysis demonstrated that old age (>60 years), lymph node (N3) and distant metastases were independent factors for poor survival, whereas radiotherapy and surgery were independent factors for favorable survival. The prognostic nomogram was established base on these five independent prognostic factors (C-index = 0.70; 95% CI 0.66-0.74). In addition, no significant difference in survival time between nasopharyngeal LEC and non-nasopharyngeal LEC patients were observed. Conclusions: LEC of the oral cavity and pharynx is a rare disease, and old age, lymph node and distant metastases, surgery and radiotherapy were significantly associated with prognosis. The prognostic nomogram could be used to make individual predictions of OS.

Keywords: Lymphoepithelial carcinoma, the oral cavity and pharynx, outcomes, SEER database, nomogram

Introduction

Lymphoepithelial carcinoma (LEC) is an uncommon malignant tumor which is defined as a carcinoma composed of undifferentiated malignant epithelial cells surrounded or infiltrated by a prominent component of characteristic lymphocytes and plasma cells; LEC accounts for approximately 5% of head and neck cancers [1, 2]. LEC was first described in the nasopharynx in 1921, and is mostly located in the nasopharynx, where it represents 40% of all nasopharyngeal neoplasms [3]. Aside from the nasopharynx, this disease can also occur in other locations, including the oral cavity, salivary glands, parotid glands, etc. A previous study reported that the incidence of salivary LEC is second to nasopharyngeal LEC, but salivary LEC is exceedingly rare and comprises only 0.4% of salivary cancers [4, 5].

The etiopathogenesis of LEC is not fully clear, tobacco smoking and alcohol consumption are identified to be contributing factors for its development. Nasopharyngeal LEC is almost invariably associated with Epstein-Barr virus (EBV) infection, and human papillomavirus (HPV) has also been identified to be a link to

LEC of the larynx, hypopharynx and oropharynx [6, 7]. Previous studies have demonstrated that LEC has significant lymphocytic infiltration that can cause a strong immune response, thus, LEC patients are always accompanied with good prognosis [8, 9]. LEC is believed to be more radiosensitive, radiotherapy as the single modality of treatment for locoregional LEC has been described. The combination of surgery and postoperative radiotherapy has been recommended for some non-nasopharyngeal LEC patients [8].

However, knowledge of LEC is currently limited to case reports and small case series, especially non-nasopharyngeal LEC. The clinicopathological characteristics and survival of nasopharyngeal LEC and non-nasopharyngeal LEC of the oral cavity and pharynx have not been well defined. Therefore, we performed a retrospective analysis of patients with LEC of the oral cavity and pharynx registered in SEER database to present the clinicopathological characteristics and prognosis. The characteristics and prognoses of nasopharyngeal LEC and non-nasopharyngeal LEC were also compared. Moreover, we constructed a prognostic nomogram to help physicians make individualized survival predictions.

Methods and materials

Participants

All patients with a diagnosis of LEC (ICD-O-3: 8310/3, ICD-O-3/WHO 2008) located in the oral cavity and pharynx between 1988 and 2013 were identified from the SEER database. The inclusion criteria: patients with primary LEC as their only cancer. The demographic information and clinicopathological characteristics of these patients were extracted using SEER*Stat software including age at diagnosis, sex, race, primary site, pathological grade, SEER historic stage A, TNM stage, and the use of surgery, radiation and chemotherapy. The overall survival information was identified and extracted from SEER database as the endpoint of this study [10, 11]. Due to the retrospective nature of the study and data from a de-identified public database, the present study was exempt from review by the ethics committee [12, 13].

Statistical analysis

Continuous data were compared using Student's t-test, while categorical data were examined using chi-square test. To compare the differences in survival time between nasopharyngeal LEC and non-nasopharyngeal LEC patients, we conducted the propensity-matching (PSM) analysis with a 1:1 ratio based on age, race, pathological grade, TNM stage, and the use of surgery, radiotherapy and chemotherapy. The Kaplan-Meier method and log-rank test was used to evaluate the influence of each variable on overall survival. Univariate Cox regression survival analysis was utilized to assess the association of each variable with prognosis, while multivariate Cox survival analysis was further performed to identify the independent prognostic factors using the significant variables from univariate analysis. The independent prognostic factors in the multivariate Cox analysis were included to construct the prognostic nomogram. All statistical analysis was performed using MedCalc software (version 15.2.2, Mariakerke, Belgium) and R 3.1.3 software (http://www.r-project.org). $P<0.05$ was considered as statistically significant.

Results

Patients' characteristics

Totally, 1025 patients with LEC of the oral cavity and pharynx were identified. **Table 1** depicts the characteristics of these patients and their treatment regimens. The lesions of most patients (769/1025) were located in the nasopharynx, while the non-nasopharyngeal LECs were observed in the salivary gland (108/1025), tonsil (79/1025), tongue (38/1025), and other sites (31/1025).

Patient survival

The median OS (mOS) of LEC patients was 232.0 months (95% CI 169.0-258.0, **Figure 1A**). The 1-, 5-, 10- and 20-year survival rates were 92.9%, 72.9%, 59.3%, and 46.8%, respectively. LEC patients with stage IV had the poorest prognosis, with a 5-year OS rate of 61.0%, compared with 92.3% for stage I, 84.6% for stage II, and 78.0% for stage III

Table 1. Characteristics of the 1025 patients with lymphoepithelial carcinoma of the oral cavity and pharynx

Characteristics	Total
Age (Year)	48.6±16.6
≤40	285
41-50	272
51-60	236
61-70	135
≥71	97
Gender	
Female	304
Male	721
Ethnicity	
White	495
Black	101
Other	420
Unknown	9
Pathological Differentiation	
Well	3
Moderate	6
Poor	234
Undifferentiated	522
Unknown	260
SEER historic stage A	
Distant	68
Regional	521
Localized	97
Unstaged	339
Primary Site	
Nasopharynx	769
Parotid Gland	108
Tonsil	79
Tongue	38
Other	31
Tumor Size	
T1	130
T2	116
T3	80
T4	63
Unknown	636
Lymph Node Metastases	
N0	94
N1	136
N2	145
N3	45
Unknown	605
Distant Metastases	
M0	385
M1	33
Unknown	607
TNM stage	
I	33
II	94
III	104
IV	166
Unknown	628
Surgery	
Yes	331
No	687
Unknown	7
Chemotherapy	
Yes	684
No/Unknown	341
Radiation	
Yes	892
No	118
Unknown	15

Ethnicity/other: American Indian/AK Native/Asian/Pacific Islander.

(**Figure 1B**). Similarly, LEC patients with distant stages had significantly worse prognoses compared to individuals with localized or regional stage according to the SEER historic stage A (P<0.01 for both); patients diagnosed with distant stage had a 5-year OS rate of 58.7%, 74.0% for localized stage and 80.0% for regional stage patients, respectively (**Figure 1C**). The prognoses of LEC patients became much worse with increasing age, increasing tumor stage and lymph node invasion (P<0.01 for all, **Figure 2A-C**). Similarly, the mOS of LEC patients with distant metastases was significantly shorter than those without distant metastases (P<0.01). The mOS of LEC patients with distant metastases was only 30 months (95% CI 12.0-43.0) (**Figure 2D**). LEC patients who were black had shorter overall survival than those who were white or other ethnicities (P<0.05 for both, Supplementary Figure 1). Besides, no significant association of other variables and survival could be observed.

Effect of different treatments on prognosis

As seen in **Figure 3A**, surgery could significantly prolong the mOS of LEC patients (255 months vs. 190 months; P<0.01). LEC patients who received radiotherapy had longer survival than those without radiotherapy (P<0.01, **Figure 3B**). The mOS of LEC patients without radiotherapy was only 76 months (95% CI 43.0-

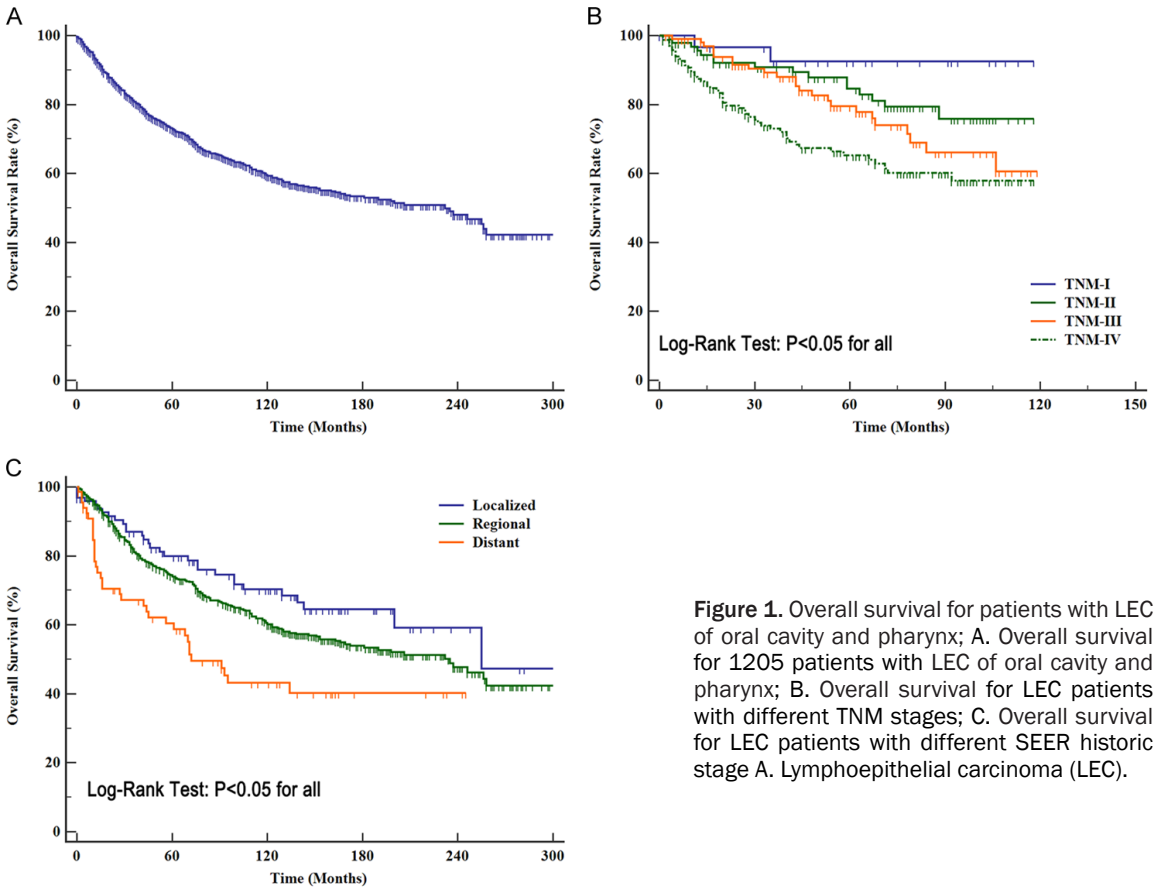

Figure 1. Overall survival for patients with LEC of oral cavity and pharynx; A. Overall survival for 1205 patients with LEC of oral cavity and pharynx; B. Overall survival for LEC patients with different TNM stages; C. Overall survival for LEC patients with different SEER historic stage A. Lymphoepithelial carcinoma (LEC).

138.0). However, no significant association between chemotherapy and overall survival could be observed (P = 0.27). A total of 18 LEC patients received radiotherapy prior to surgery, while 239 patients received radiotherapy after surgery. The survival analysis showed that the combination of radiotherapy with surgery could significantly improve the patients' prognoses compared with those with surgery alone (P<0.01) (**Figure 3C**).

Univariate and multivariate Cox proportional hazard analyses

Table 2 showed the variables that could potentially influence OS using univariate Cox survival analysis. Old age, black ethnicity, large tumor stage, lymph node and distant metastases, and late TNM stages were significantly associated with poor prognosis, while the use of radiotherapy and surgery was related to good prognosis (P<0.05 for all, **Table 2**). Subsequently, the multivariate Cox survival analysis demonstrated that only old age (>60 years), lymph node (N3) and distant metastases (M1) were independent factors for poor prognosis, whereas radiotherapy and surgery were independent factors for favorable survival among LEC patients (**Table 2**).

Prognostic nomogram for LEC patients

To make an individualized survival prediction of LEC patients, we established a prognostic nomogram using all independent prognostic factors from the multivariate Cox survival analysis (**Figure 4**). The nomogram illustrated that M category had the largest effect on OS, followed by age and N category. Tumor stage, race and the use of surgery and radiotherapy showed a moderate effect on prognosis. The calibration plots for the probability of overall survival at 3, 5 or 10 years in the LEC patient cohort yielded an optimal consistency between the prediction survival and the actual observation. The C-index for survival prediction in this prognostic nomogram was 0.70 (95% CI 0.66-0.74).

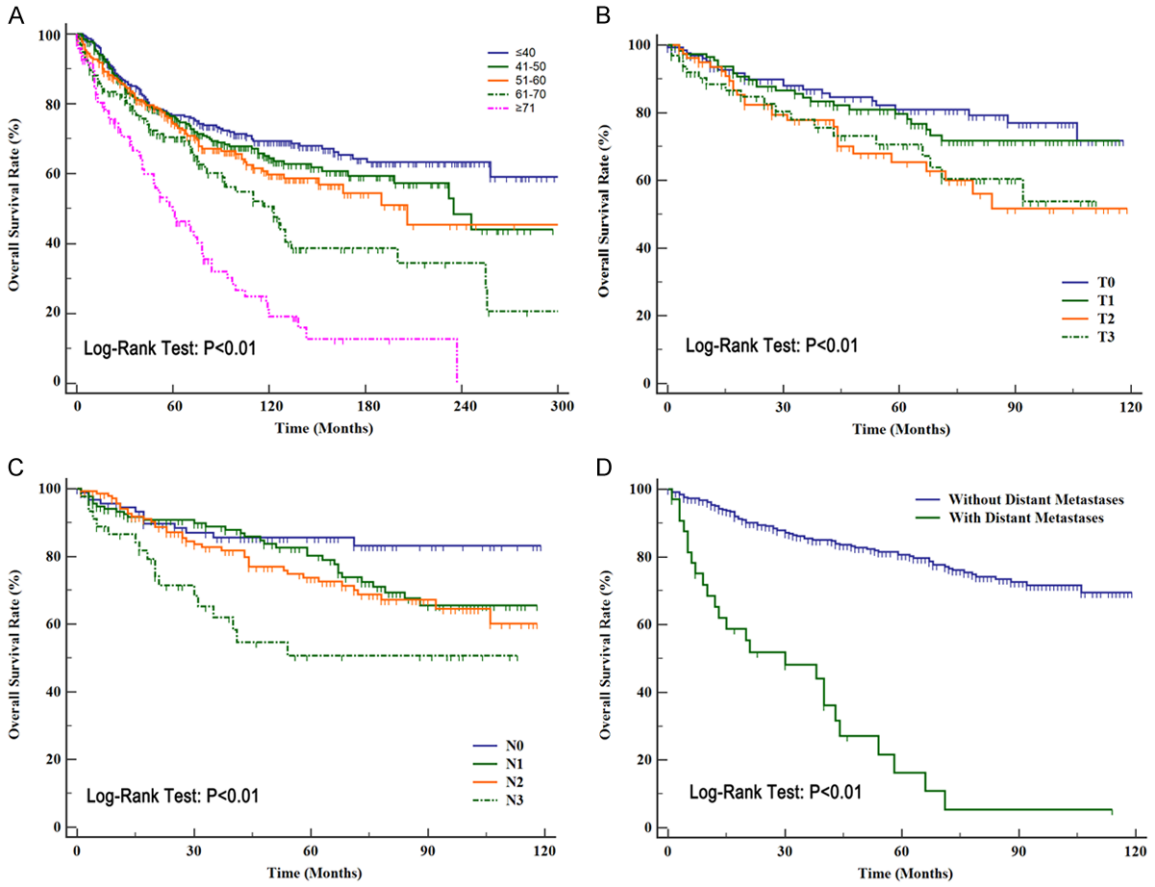

Figure 2. Overall survival for patients with LEC of oral cavity and pharynx; A. overall survival stratified by age; B. tumor stage; C. lymph node metastases; D. distant metastases. Lymphoepithelial carcinoma (LEC).

Comparative analysis of nasopharyngeal LEC and non-nasopharyngeal LEC

Supplementary Table 1 depicts the characteristics of the nasopharyngeal LEC and non-nasopharyngeal LEC patients. Non-nasopharyngeal LEC patients were more likely to be young, male and have an undifferentiated grade, late TNM stage than nasopharyngeal LEC patients, while nasopharyngeal LEC patients were more likely to be of American Indian/AK Native/Asian/Pacific Islander descent than non-nasopharyngeal LEC patients. For treatment option, non-nasopharyngeal LEC patients were more likely to receive surgery, radiation and chemotherapy than nasopharyngeal LEC patients. In the survival analysis stratified by primary site, the mOS of nasopharyngeal LEC patients was 235 months (95% CI 160.0-258.0), which was longer than that of non-nasopharyngeal patients (Mos = 200 m, 95% CI 143.0-256.0), but without statistically significant difference (P = 0.17, **Figure 5A**). To exclude the influence of confounding factors, we carried out a PSM analysis to balance the characteristic and treatment regimen between these two groups. A total of 96 non-nasopharyngeal LEC patients were matched with 96 nasopharyngeal LEC patients (1:1) after PSM analysis (Supplementary Table 2). The survival analysis demonstrated that the survival of non-nasopharyngeal LEC patients was slightly better than that of nasopharyngeal LEC patients, but without statistical significance (166.0 m vs 90.0 m, P = 0.20, **Figure 5B**). Both the univariate Cox analysis and multivariate Cox analysis revealed that location was not significantly associated with the prognosis of LEC patients.

Discussion

The majority of lymphoepithelial carcinoma studies was comprised of case reports or small

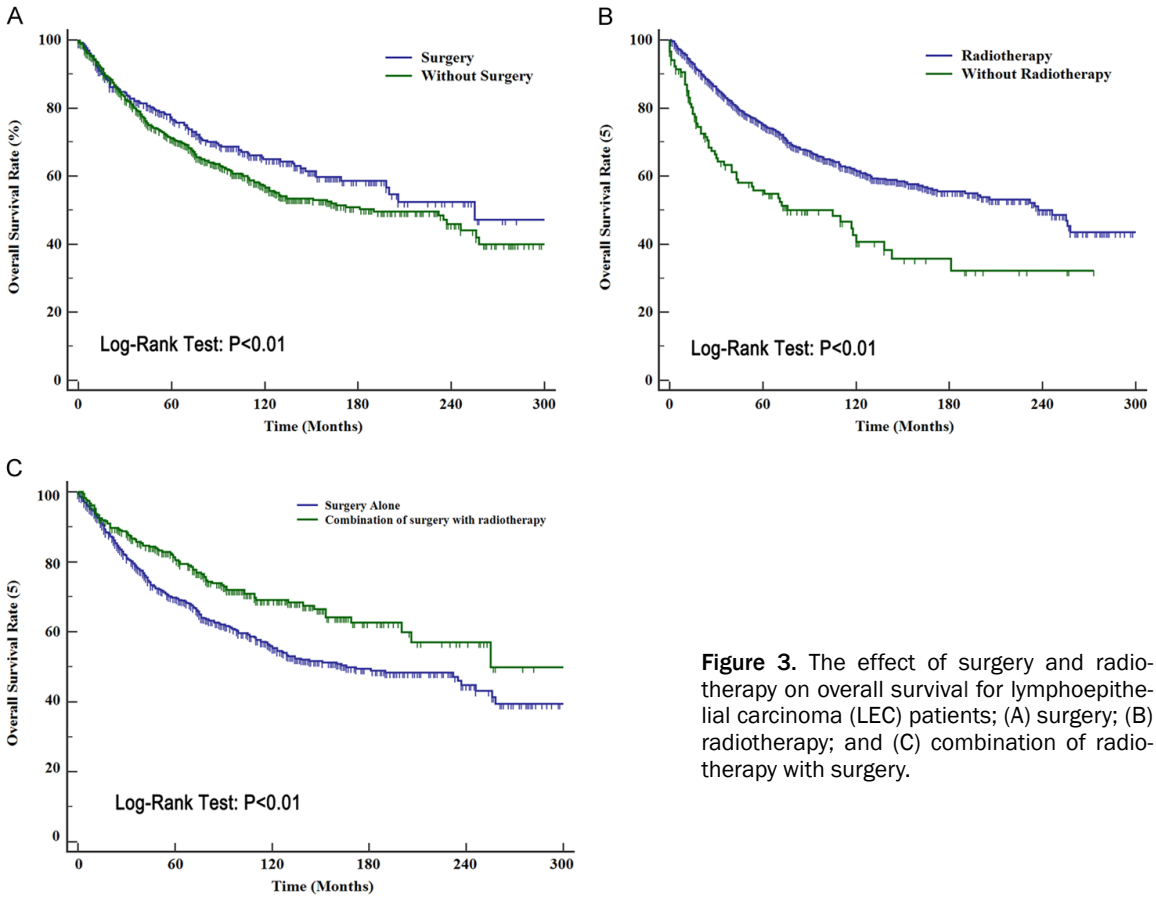

Figure 3. The effect of surgery and radiotherapy on overall survival for lymphoepithelial carcinoma (LEC) patients; (A) surgery; (B) radiotherapy; and (C) combination of radiotherapy with surgery.

series due to the rarity of this condition, especially non-nasopharyngeal LEC such as salivary gland LEC, tonsil ELC, laryngeal LEC, etc [14-16]. Therefore, the clinicopathological characteristics and survival of this disease were not fully clear, especially regarding the differences between nasopharyngeal LEC and non-nasopharyngeal LEC. In the present study, we described the clinicopathological characteristics and prognosis of this disease and determine the factors that affect survival based on the data of 1205 patients from the SEER database. We also conducted a comparison analysis of patients with nasopharyngeal LEC and non-nasopharyngeal LEC. Furthermore, we constructed a prognostic nomogram for patients with LEC of the oral cavity and pharynx to make an individualized survival prediction.

Nasopharyngeal LEC is most commonly found in the oral cavity and pharynx. Our data showed that 75.0% of LEC was located in the nasopharyngeal area. Patients with nasopharyngeal LEC are young, with an average age of 45.8 years. Previous studies have reported several pediatric patients with nasopharyngeal carcinoma [17, 18]. Nasopharyngeal LEC patients were predominantly male, with a male to female ratio of 2.73:1. Moreover, our data showed that the incidence of nasopharyngeal LEC is much higher in the non-white/black population. This is attributed to the prevalence and distribution of cancer-related viruses, such as EBV and HPV [19, 20]. Nasopharyngeal LEC patients can remain asymptomatic for a long time because the nasopharynx is a clinically occult site. Nonspecific symptoms often cause delay a in definitive diagnosis, one case series reported a mean delay period of 7.2 months [21]. Consequently, more than 90% of nasopharyngeal LEC patients present locally or regionally advanced disease [22]. Additionally, the previous studies provide data from patients who had a high incidence of distant metastases, ranging from 20% to 40% [23, 24]. In our study, 91.5% of nasopharyngeal LEC patients had regional or distant metastases, and 81.0% of cases had lymph node metastases. Due to

Table 2. Univariate and multivariate Cox proportional hazard analyses of the clinical characteristics for overall survival rates in patients with lymphoepithelial carcinoma of the oral cavity and pharynx

Factor	Category	Univariate		Multivariate	
		HR (95% CI)	p-*Participants*	HR (95% CI)	*p*-value
Age	≤40	Reference		Reference	
	41-50	1.24 (0.92-1.66)	0.16	1.01 (0.53-1.94)	0.96
	51-60	1.40 (1.04-1.90)	0.03	0.90 (0.46-1.94)	0.75
	61-70	2.03 (1.47-2.82)	<0.01	1.91 (1.01-3.68)	0.04
	≥71	3.80 (2.74-5.29)	<0.01	4.49 (2.11-9.56)	<0.01
Gender	Female	Reference			
	Male	1.19 (0.95-1.49)	0.13		
Race	White	Reference			
	Black	1.56 (1.14-2.14)	<0.01		
	Other	1.05 (0.85-1.30)	0.66		
Pathological Differentiation	Poor	Reference			
	Undifferentiated	1.08 (0.84-1.38)	0.55		
SEER historic stage A	Localized	Reference			
	Regional	1.33 (0.91-1.95)	0.14		
	Distant	2.30 (1.41-3.73)	<0.01		
Primary Site	Nasopharynx	Reference			
	Non-nasopharynx	0.85 (0.66-1.18)	0.17		
	Parotid Gland	0.84 (0.55-1.17)	0.25		
	Tonsil	0.69 (0.44-1.08)	0.11		
	Tongue	0.75 (0.40-1.41)	0.37		
	Other	1.30 (0.83-2.04)	0.25		
Tumor	T1	Reference			
	T2	1.23 (0.70-2.16)	0.47	1.39 (0.78-2.48)	0.27
	T3	2.08 (1.19-3.63)	0.01	1.79 (0.96-3.34)	0.06
	T4	2.02 (1.11-3.71)	0.02	1.39 (0.70-2.75)	0.34
Lymph Node Metastases	N0	Reference			
	N1	1.64 (0.87-3.12)	0.13	1.18 (0.57-2.42)	0.66
	N2	1.90 (1.15-3.55)	0.04	1.67 (0.85-3.30)	0.14
	N3	3.72 (1.83-7.56)	<0.01	3.63 (1.56-8.48)	<0.01
Distant metastases	Yes/No	6.98 (4.45-11.0)	<0.01	6.02 (3.16-11.5)	<0.01
Surgery	No/Yes	0.80 (0.65-0.79)	<0.01	0.65 (0.37-0.99)	0.04
Radiation	No/Yes	0.51 (0.36-0.74)	0.02	0.76 (0.41-0.92)	0.03
Chemotherapy	Yes/No+Unknown	0.89 (0.72-1.10)	0.27		

anatomical limitations on surgical interventions, radiotherapy is undoubtedly the preferred choice of treatment and chemotherapy is combined in advanced disease [24]. For example, in the present study, only 20.8% of nasopharyngeal LEC patients underwent surgery, whereas 72.8% patients received chemotherapy, and 90.6% patients received radiotherapy.

Compared with nasopharyngeal LEC, non-nasopharyngeal LEC is much rarer. Until now, a few large case series have been reported. Ma et al. reported a cohort of 69 salivary gland LEC patients in China [8], while Dubey et al. reported 34 non-nasopharyngeal LEC patients in the United States between 1950 and 1994 [25]. In 2016, Chan JY et al. reported 378 patients with non-nasopharyngeal LEC from the SEER database [26]. In 2020, Wang et al reported a cohort of 179 salivary gland LEC patients from the SEER database [5]. All of these studies suggested that non-nasopharyngeal LECs were often located in the oropharynx, salivary gland, tonsil, and tongue, etc. Chan JY and Dubey

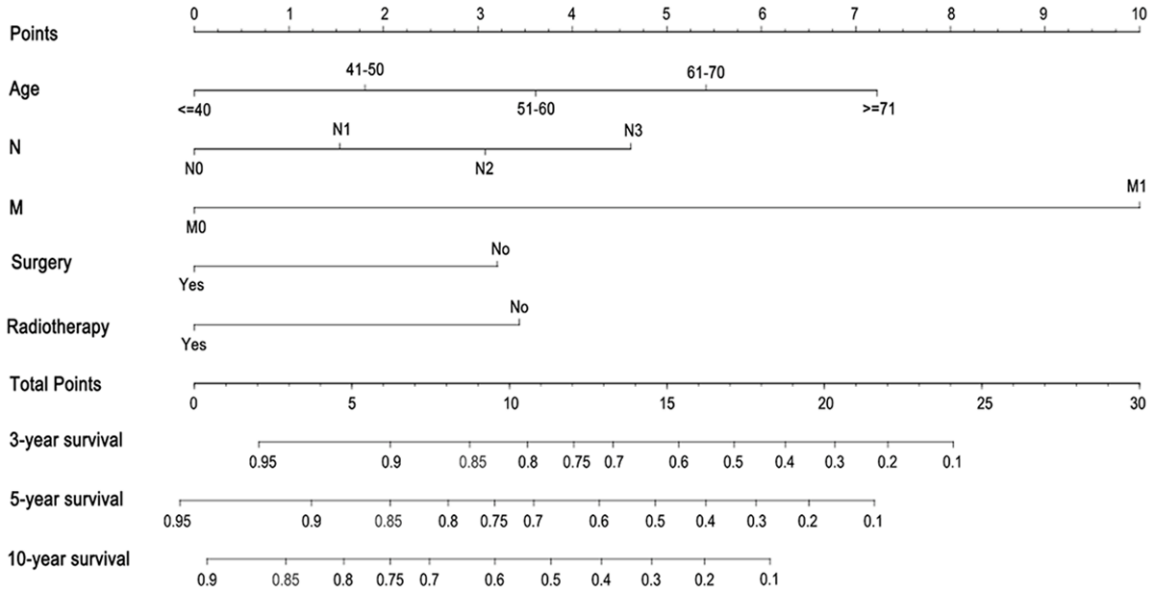

Figure 4. Prognostic Nomogram calculated by clinical characteristics for 3-years, 5-years, 10-years survival in patients with lymphoepithelial carcinoma (LEC) of oral cavity and pharynx.

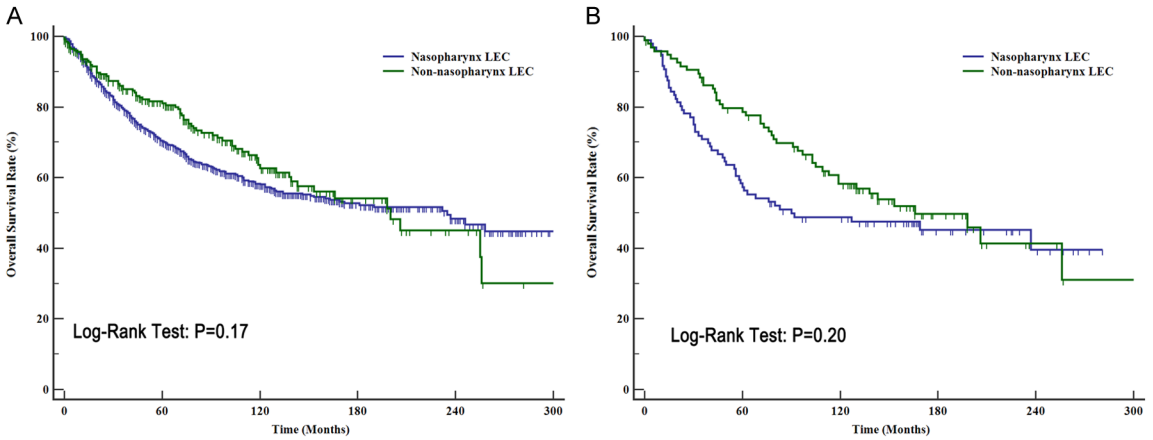

Figure 5. Comparative analysis of overall survival for nasopharynx Lymphoepithelial carcinoma (LEC) patients and non-nasopharynx LEC patients; (A) in unmatched cohort and (B) in matched cohort.

reported that the primary occurrence was in an oropharyngeal site in the majority of cases, followed by the salivary gland [26], while the present study found that the salivary gland was the most common site of non-nasopharyngeal LEC. One possible reason behind this discrepancy is the difference in time span. Chan JY and Dubey's studies recruited patients from 1950 to 1994 and 1973-2011, respectively. Our study retrospectively analyzed LEC patients from 1988 to 2013. The other reason is the diagnosis of LEC. In Chan JYK's study, they included all non-nasopharyngeal LEC patients, while our study identified patients with only primary non-nasopharyngeal LEC. In addition, the clinical characteristics of non-nasopharyngeal LEC patients from the present study are consistent with those of previous reports. Our study found that most non-nasopharyngeal patients were men, with a male to female ratio of 1.6:1. Most non-nasopharyngeal LEC patients were aged younger than 60 years (62.5%) and were white (72.7%). Lymph node metastases in non-nasopharyngeal LEC are common with the incidence ranged from 10% to 50%. In the present study, the incidence of lymph node metastases

was 70.2%, which is much higher than that from previous studies. One possibility for this discrepancy is that the lymph node status of 125 out of the 256 (48.8%) non-nasopharyngeal LEC patients was unknown in the present study. In addition, most non-nasopharyngeal LEC patients had advanced-stage (III/IV) disease, ranging from 59.4% to 80.2% at diagnosis in these studies. Our data reported that 78.2% patients were diagnosed with advanced stage. In our cohort, 186 patients were white; in contrast, 53 cases of advanced-stage disease occurred in patients who were nonwhite, including American Indian/AK Native, Asian/Pacific Islander. Our findings support those of Chan JY, who identified that 23.7% of their non-nasopharyngeal LEC patients were nonwhite/black.

A strong association of EBV with LEC has been reported in Southeast Asia, Greenland, and Alaska, but not in the white population, especially for salivary gland LEC [8, 27, 28]. Several previous studies from high incidence regions have observed EBV positivity in non-nasopharyngeal LEC cases; for example, Ma reported that all 38 Chinese salivary gland LEC cases with EBV encoded RNA positive [8]. One potential explanation is associated with the geographic distribution of the 2 major types of EBV. Type 1 EBV is the most prevalent type worldwide, whereas type 2 EBV is only common in certain areas such as Alaska, where there is a much higher incidence of salivary gland LEC. Although the present study did not analyze the EBV status in LEC patients due to inadequate information from SEER database, the 5-year OS of non-nasopharyngeal LEC was 81.1%, which is relatively lower than 90% reported by Ma et al., thus suggesting a difference in etiology and a different relationship with EBV. Besides, previous studies did not support a positive relationship of EBV with other non-nasopharyngeal, non-salivary gland LECs. For example, Singhi et al. found that all 22 patients with oropharynx LEC were HPV-P16 positive rather than EBV [7]. Chow et al. also reported 5 patients with intraoral LEC who were EBV negative. Of course, this relationship requires further validation in the future.

With the development of molecular biology, an increasing number of potential biomarkers have been identified for LEC development. Previous studies have demonstrated the molecular signature of LEC including BCL-2 overexpression, low rates of EGFR mutation, absence of HER2 and p53 expression [26]. BCL-2 overexpression may also render LEC patients sensitive to treatment with chemotherapeutic agents that target the apoptotic pathways associated with BCL-2 [29]. In our cohort, 684 of 1205 LEC patients received chemotherapy, and the prognosis survival showed that chemotherapy could prolong overall survival of LEC patients, but without significantly statistical differences. Because 341 LEC patients did not have accurate chemotherapy information, the role of chemotherapy in LEC needs to be confirmed in a large cohort. Because of the similarities between the histology of LEC and nasopharyngeal carcinoma, the chemotherapy regimens commonly used for NPC may also work in LEC patients. The low occurrence rate of EGFR mutations and HER2 expression limits the utility of EGFR-TKIs as well as anti-HER2 antibodies. However, patients who received those treatments often have a good prognosis [9]. Similar to NPC, LEC of the oral cavity and pharynx has been demonstrated to be sensitive to radiotherapy. In the present study, radiotherapy could significantly improve the prognosis of LEC patients, and radiotherapy could decrease the risk of death by 49%. Postoperative radiotherapy was recommended for indications including non-R0 resection, stage T4, and lymph node metastases. In our cohort, 16.2% and 77.6% of LEC patients were diagnosed with T4 stage and lymph node metastases, respectively. Radiotherapy after surgery could significantly prolong the survival of LEC patients who underwent surgery. In addition, the prognostic and therapeutic importance of EBV positivity and PD-L1 expression in nasopharyngeal carcinoma requires an investigation on whether LEC can be a potential immunotherapy target, similar to nasopharyngeal carcinoma, which has a strong immune response. Theoretically, lymphocyte compounds should be observed in the LEC tumor environment, and immunotherapy through the inhibition of immune suppression, such as through PD-L1 inhibitors, has promising prospects for LEC treatment.

In accordance with other reports, we found that patients with LEC of the oral cavity and pharynx had a much better prognosis. Almost 50% of the LEC patients could survive for 20 years in our cohort. In addition, the survival analysis in both unmatched cohort and matched cohort

did not yield any significant difference in survival time between nasopharyngeal LEC and non-nasopharyngeal LEC patients. Therefore, we constructed a prognostic nomogram for individualized survival prediction of LEC patients using the long-term follow-up data from the SEER database. With this easy-to-use scoring system, both physicians and patients could calculate the survival probability of individual LEC patients. When a prognostic nomogram is completed, the validation of the nomogram is essential to avoid overfitting the model and determine its generalizability [30-32]. For common cancers, validation of the prognostic nomogram should be performed in the primary cohort and an independent cohort. However, this prognostic nomogram for LEC patients can only be validated in the primary cohort due to the rarity of LEC. In addition, several important prognostic indices were not included in this prognostic nomogram such as serum tumor markers and we only included the patients from SEER database between 1988 and 2013 to observe more study endpoints due to the favorable prognosis of this disease. Further studies with more comprehensive information are required to confirm the accuracy of this nomogram.

In the present study, we described the clinicopathological characteristics and survival of patients with LEC of the oral cavity and pharynx. The results showed that patients with LEC of the oral cavity and pharynx often had a favorable prognosis. Old age, lymph node and distant metastases, surgery and radiotherapy were significantly associated with prognosis. Non-nasopharynx LEC patients were more likely to be young and male and have an undifferentiated grade and late TNM stage, but there was not any significant difference in prognosis between nasopharyngeal LEC and non-nasopharyngeal LEC patients that was observed. Meanwhile, we also constructed the first prognostic nomogram to predict individual survival. In conclusion, the present study is the largest series concerning LEC of the oral cavity and pharynx, and these results are vital to disease management and future prospective studies for this rare cancer.

Disclosure of conflict of interest

None.

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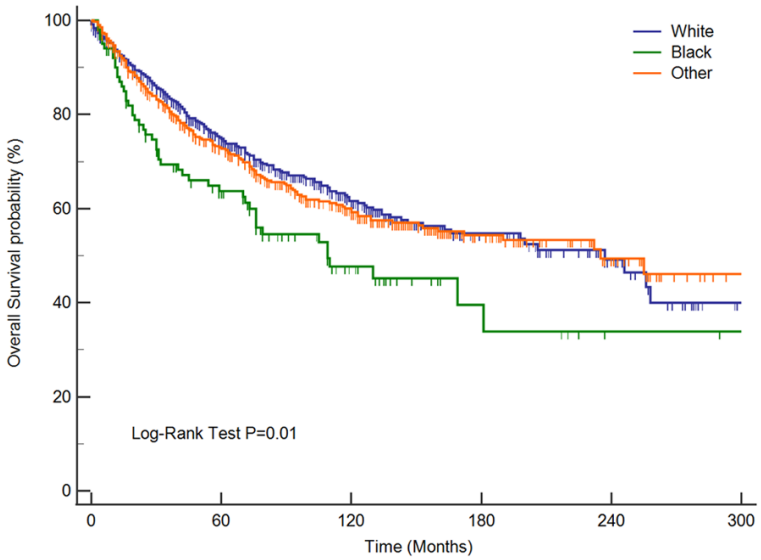

Supplementary Figure 1. Overall survival stratified by race.

Supplementary Table 1. Characteristics of nasopharynx LEC patients and non-nasopharynx LEC patients

Characteristics	Nasopharynx (N=769)	Non-nasopharynx (N=256)	*P* value
Age (Year)	45.8±16.4	56.8±14.5	<0.01
≤40	256	29	<0.01
41-50	217	55	
51-60	160	76	
61-70	87	48	
≥71	49	48	
Gender			
Male	563	131	<0.01
Female	206	81	
Ethnicity			
White	309	186	<0.01
Black	86	15	
Other	367	53	
Unknown	7	2	
Pathological Differentiation			
Well	0	3	<0.01
Moderate	2	4	
Poor	145	89	
Undifferentiated	437	85	
Unknown	185	75	
Summary Stage			
Distant	50	47	<0.01
Regional	350	171	
Localized	37	31	
Unstaged	332	7	

Tumor Stage			
T1	102	28	<0.01
T2	73	43	
T3	58	22	
T4	44	19	
Unknown	492	144	
Lymph Node Metastases			
N0	55	39	<0.01
N1	110	26	
N2	85	60	
N3	39	6	
Unknown	480	125	
Distant Metastases			
M0	257	128	<0.01
M1	30	3	
Unknown	482	125	
TNM stage			
I	24	9	<0.01
II	76	18	
III	82	22	
IV	91	75	
Unknown	496	132	
Surgery			
Yes	159	172	<0.01
No	605	82	
Unknown	5	2	
Chemotherapy			
Yes	560	124	<0.01
No/Unknown	209	132	
Radiation			
Yes	686	206	<0.01
No	71	47	
Unknown	12	3	

LEC, Lymphoepithelial carcinoma.

Supplementary Table 2. Characteristics of nasopharynx LEC patients and non-nasopharynx LEC patients after PSM analysis in matched cohort

Characteristics	Nasopharynx (N=96)	Non-nasopharynx (N=96)	*P* value
Age (Year)			
≤40	19	11	0.614
41-50	27	28	
51-60	24	28	
61-70	10	12	
≥71	16	17	
Gender			
Male	71	62	0.211
Female	25	34	

Ethnicity			
White	48	50	
Black	9	8	0.82
Other	37	37	
Unknown	2	1	
Pathological Differentiation			
Well	0	3	
Moderate	2	4	
Poor	145	89	
Undifferentiated	437	85	
Unknown	185	75	
Summary Stage			
Distant	8	10	0.91
Regional	69	71	
Localized	11	8	
Unstaged	7	7	
Tumor Stage			
T1	2	2	
T2	1	1	1.000
T3	1	1	
T4	0	0	
Unknown	92	92	
Lymph Node Metastases			
N0	1	1	
N1	0	1	0.92
N2	3	2	
N3	1	1	
Unknown	91	90	
Distant Metastases			
M0	3	2	
M1	1	1	0.86
Unknown	92	93	
TNM stage			
I	24	9	
II	76	18	
III	82	22	
IV	91	75	
Unknown	496	132	
Surgery			
Yes	57	60	
No	39	35	0.524
Unknown	0	1	
Chemotherapy			
Yes	65	56	
No/Unknown	31	40	
Radiation			
Yes	84	84	1.00
No	12	12	
Unknown	0	0	

LEC, Lymphoepithelial carcinoma.