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Lymphoepithelial carcinoma of the head and neck: a SEER analysis of prognostic factors for survival

Jing Wei[1,*], Hui Deng[2,*], Lihua Wu[1], Jianbo Song[1], Junping Zhang[1], Wenhui Yang[1], Mengxian Zhang[1,2] and Hongtao Zhen[3]

Abstract

Objective: To explore the epidemiological characteristics of patients with lymphoepithelial carcinoma (LEC) of the head and neck and the prognostic factors.

Methods: We conducted a retrospective cohort study of cases of head and neck LEC retrieved from the Surveillance, Epidemiology and End Results database. Kaplan–Meier survival analysis and the log-rank test were employed to assess overall survival (OS) and cancer-specific survival (CSS). Univariate and multivariate analyses were used to construct Cox regression models. We established nomograms to predict OS and CSS among patients with nasopharyngeal LEC, who were divided into high- and low-risk groups based on the OS nomograms to compare the effects of treatment using the restricted mean survival time (RMST).

Results: The 5-year OS and CSS rates of the cohort were 70.8% and 74.8%, respectively. Advanced age, unmarried status, black race, distant metastasis, and the absence of surgical treatment were significantly associated with decreased survival rates. RMST did not differ between the combined treatment (radiotherapy and chemotherapy) and radiotherapy monotherapy groups, but chemotherapy alone displayed poor efficacy.

Conclusions: Head and neck LEC is associated with a favorable prognosis. Radiotherapy plays a significant role in managing patients with nasopharyngeal LEC, which is influenced by multiple prognostic factors.

[1]Cancer Center of Shanxi Bethune Hospital, Shanxi Academy of Medical Science, Taiyuan, China
[2]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China
[3]Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

*These authors contributed equally to this work, and they should be considered co-first authors.

Corresponding author:
Hongtao Zhen, Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, 1095 Jiefang Avenue, Qiaokou District, Wuhan, Hubei, China.
Email: zhttj123@126.com

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Introduction

As a rare malignancy, lymphoepithelial carcinoma (LEC) of the head and neck histologically comprises malignant epithelial cells with characteristic lymphoid stroma. Notably, most cases of LEC are related to Epstein–Barr virus infection.[1–3] LEC is more common in men than in women, and it predominantly occurs in people aged 50 to 70 years.[4–8] Head and neck LEC is a heterogeneous disease with a panoply of clinical manifestations at different onset locations, including the oropharynx, laryngopharynx, and salivary glands.[9–11] However, most cases occur in the nasopharynx, and they are classified pathologically as non-keratinizing undifferentiated nasopharyngeal carcinoma.[12] In addition, LEC preferentially arises in people of Eskimo, Chinese, and Japanese ethnicity.[8] Tobacco smoking and alcohol consumption are considered the potential precipitating factors of LEC.[4] The existing literature regarding head and neck LEC mostly consists of case reports and small-scale retrospective analyses, but large-scale population-based studies are rare. Surveillance, Epidemiology, and End Results (SEER), a large-scale tumor registration database in the United States, has accumulated substantial clinical evidence about rare malignant tumors such as LEC. In this study, we retrieved cases of head and neck LEC from the SEER database and reviewed the issues associated with survival and the related prognostic factors.

Materials and methods

Data source and subjects

Because LEC is rare, the research data for this work were extracted from the SEER-9 registry database (1975–2016). We retrieved a substantial number of cases to explore the survival characteristics of patients with LEC. A list of cases diagnosed since 1975, including patients with head and neck LEC, was generated via SEER*Stat version 8.3.8. The primary site of the tumor (Table S1) and histology type (8082/3) were confirmed by the third edition of the International Classification of Disease for Oncology (ICD-O-3). We included patients with confirmed histopathological diagnosis ("positive histology") and specific order of primary cancer ("one primary only" and "first of two or more primaries") in the study; however, patients younger than 20 years and those with a follow-up period of 0 months were excluded. For all enrolled individuals, we retrieved information on the following variables: age at diagnosis, sex, marital status, race, year of diagnosis, location of tumor origin, SEER historical stage, grade, surgery, radiotherapy, and chemotherapy. We obtained signed authorization and permission from the SEER database to access and use the data and followed protocols throughout the process to protect patient privacy. Therefore, the requirements for ethics approval and informed consent were waived.

Processes and methods

We applied descriptive statistics to summarize subject characteristics. Through Kaplan–Meier survival analysis, the impact of different factors on overall survival (OS) and cancer-specific survival (CSS) were assessed, followed by the log-rank test for comparison. Hazards ratios (HRs) were generated via Cox regression models for univariate and multivariate analyses in all patients.

Because most included patients had nasopharyngeal LEC (72.9%) in our study, the least absolute shrinkage and selection operator (LASSO) regression model[13] and Cox multivariate regression analysis were employed to select the characteristic prognosis factors for such patients. Thereafter, we devised a nomogram model to predict 1-, 3-, and 5-year OS and CSS. Calibration curves were applied to assess the predictive accuracy of the nomogram. Patients were categorized into high- and low-risk groups based on the risk scores of the nomogram. Subsequently, the Cox regression model and restricted mean survival time (RMST) model were established to evaluate the mortality risks of the two risk groups. Moreover, we applied the RMST model to assess the effects of combined radiotherapy and chemotherapy, chemotherapy alone, and radiotherapy alone in patients in different risk groups.

Statistical analysis

Basic descriptive statistical analysis was performed via Stata version 14.0 (Stata Corporation, College Station, TX, USA). For other analyses, Rstudio version 4.0.2 was adopted. The associated software packages included "survminer," "rms," "ggplot," "glmnet," "nomogramEx," and "survRM2." Statistical significance was set at $P < 0.05$ on both sides.

Results

Characteristics of the study subjects

In total, 1398 patients with head and neck LEC (mean age, 51.8 ± 14.6 years; median age, 52 years) were enrolled in the study. Most patients were male (974, 69.7%). Notably, a higher proportion of patients (70.4%) were enrolled after 1995. Detailed patient characteristics are presented in Table 1.

The demographic and survival characteristics of patients with head and neck LEC according to the primary tumor location are summarized in Table S2. Nearly 72.9% of patients had LEC of the nasopharynx, and the mean age of these patients (49 years) was lower than that of patients with other tumor locations. Excluding LEC of the salivary glands, more patients were male than female for each tumor location. Patients with LEC of the larynx, glottis, and hypopharynx were characterized by the lowest 5-year OS (52.0%) and 5-year CSS (66.8%).

Survival analysis

The OS and CSS data for all patients with LEC of the head and neck are highlighted in Figure 1a and 1b, respectively. At the end of follow-up, 721 patients had died, 480 of whom succumbed to cancer-related diseases. According to Kaplan–Meier survival analysis, the median OS was 156 months, and the 5-year OS rate was 70.8%. Of note, OS was superior to CSS in all patients.

For subgroup analyses, we created Kaplan–Meier survival curves to compare OS and CSS (Figures 1 and S1–2). Older age was associated with worse OS and CSS. Men displayed significantly worse OS and CSS than women. White race and a married status were identified as favorable prognostic factors. Compared with

Table 1. Baseline demographic and clinicopathologic characteristics of lymphoepithelial carcinoma diagnosed in SEER 9 registries (1975–2016).

Characteristic	No. of patients	%
Total	1398	100
Age at diagnosis (years)		
Mean ± SD	51.8 (14.6)	
Median (IQR)	52 (42–62)	
20–39	269	19.2
40–59	718	51.4
60–79	367	26.3
≥80	44	3.1
Sex		
Female	424	30.3
Male	974	69.7
Marital status		
Married	916	65.5
Unmarried	407	29.1
Race		
White	702	50.2
Black	110	7.9
Asian or Pacific Islander	543	38.8
Year of diagnosis		
1975–1984	218	15.6
1985–1994	196	14
1995–2004	513	36.7
2005–2016	471	33.7
Primary site		
Oral cavity	65	4.6
Salivary glands	146	10.4
Oropharynx	149	10.7
Nasopharynx	1019	72.9
Larynx, glottis, and hypopharynx	19	1.4
SEER historical stage		
Localized	171	12.2
Regional	716	51.2
Distant	114	8.2
Grade		
Low	12	0.9
High	937	67
Surgery		
Yes	462	33
No	912	65.2
Radiation and chemotherapy		
Both	725	51.9
Radiation only	505	36.1
Chemotherapy only	47	3.4
No/unknown	121	8.7
Cancer-specific mortality		
Alive	918	65.7
Dead	480	34.3
Overall survival		
Alive	677	48.4
Dead	721	51.6
Survival time (months)		
Mean ± SD	111.2 (93.0)	
Median (IQR)	91 (33–163)	

SD, standard deviation; IQR, interquartile range.

patients diagnosed between 1975 and 1984, patients diagnosed after 1984 had significantly better OS and CSS (both $P < 0.0001$). The dismal OS and CSS of patients diagnosed before 1985 were associated with distant metastases or high-grade malignancy.

Regarding treatment (Figure S3), patients who underwent surgery or received simultaneous radiotherapy and chemotherapy exhibited longer OS and CSS than those who declined surgery or received a single treatment (radiotherapy or chemotherapy alone).

Cox multivariate regression models for all patients

To generate the Cox multivariate regression models for OS and CSS, we selected variables significant at $P < 0.05$ in Cox univariate regression models (Table S3). As presented in Table 2, older age was associated with worse OS (e.g., ≥80: HR = 6.58, 95% confidence interval [CI] = 3.09–14.00) and CSS (e.g., ≥80: HR = 2.56, 95% CI = 0.84–7.82). Unmarried patients had 1.44- (OS) and 1.60-fold (CSS) higher risks of mortality than married patients,

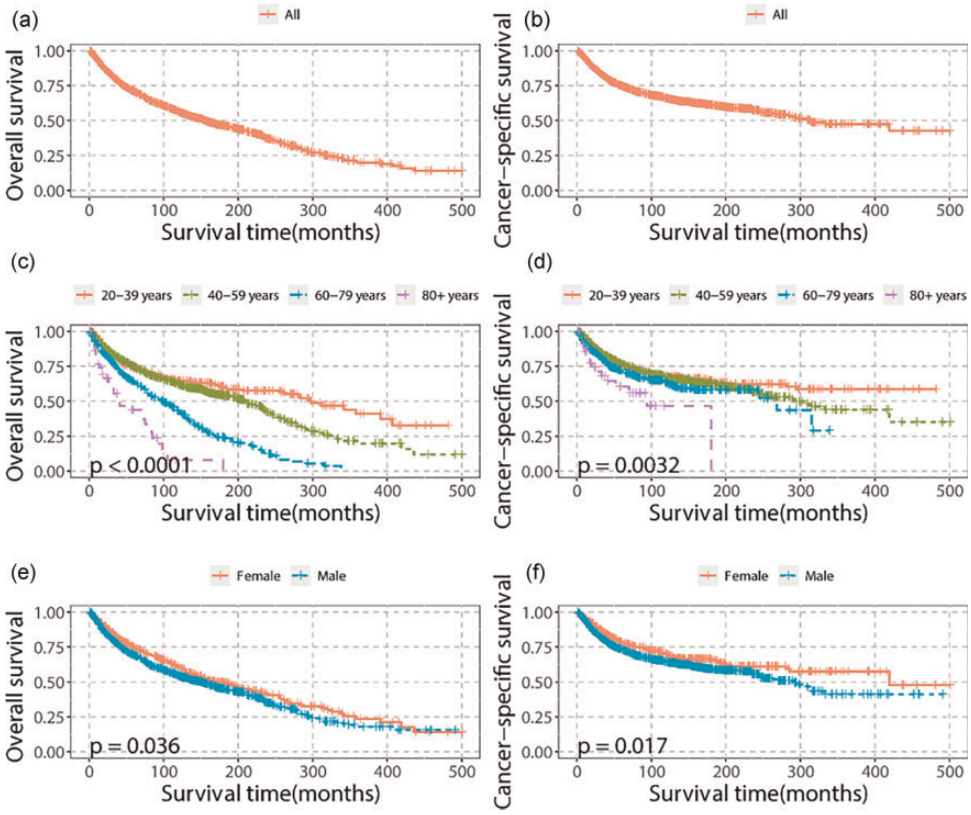


Figure 1. Survival analysis of lymphoepithelial carcinoma: (a) OS and (b) CSS are presented for all patients OS and CSS analysis stratified by age (c, d) and sex (e, f).
OS, overall survival; CSS, cancer-specific survival.

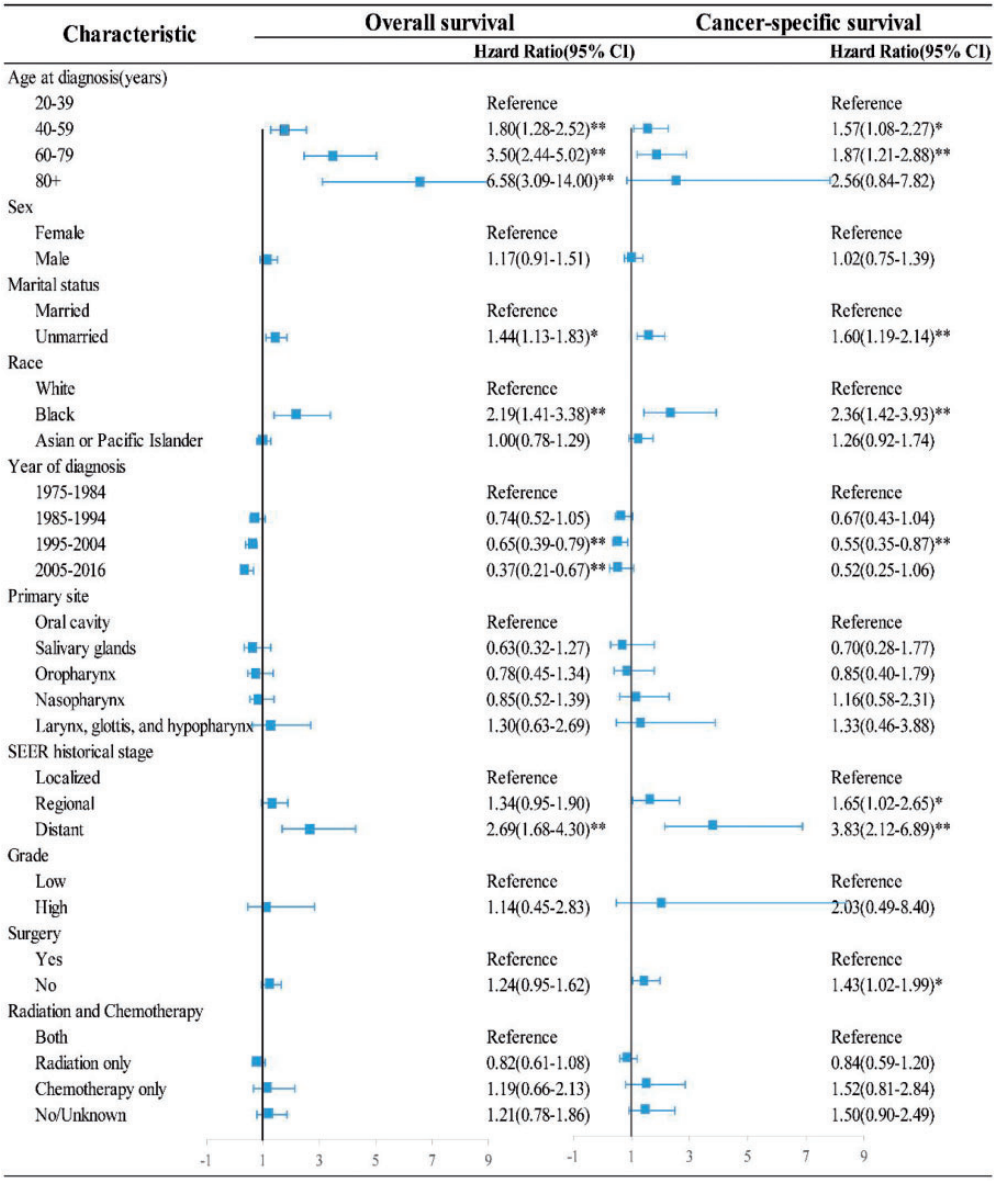
and the increased risks were statistically significant (both $P < 0.05$). Black patients had worse OS (HR = 2.19, 95% CI = 1.41–3.38) and CSS (HR = 2.36, 95% CI = 1.42–3.93) than white patients. Furthermore, the year of diagnosis, distant metastasis, and the receipt of surgery significantly impacted OS and CSS (all $P < 0.05$).

Nomograms for nasopharyngeal LEC

Because the majority of patients had nasopharyngeal LEC (72.9%), we established nomograms for clinical prediction. Using the LASSO regression model, we screened variables for predicting OS and CSS and solved the over-fitting problem caused by multicollinearity (Table S4). Notably, Yes, the operation for each characteristic provided a different result depending on the software; thus, we set the operation to repeat 1000 times to calculate the frequency of each variable. Subsequently, the selected characteristic variables with high frequencies (>800) were integrated into Cox multivariate regression models (Table S5).

The clinical prediction models for 1-, 3-, and 5-year OS and CSS (Figure 2) were constructed according to the critical predictor variables selected via LASSO regression. To evaluate the accuracy of the nomograms, we used new samples generated from bootstrap self-sampling. Theoretically, the standard calibration curve is a straight line

Table 2. Cox multivariate regression analysis of prognostic factors for OS and CSS among patients with lymphoepithelial carcinoma of the head and neck.



*$P < 0.05$, **$P < 0.01$.

passing the origin of the coordinate axis with a slope of 1. Of note, the predictive power of the line graph increases as the prediction calibration curve gets closer to the standard curve. The nomograms predicting 1-, 3-, and 5-year OS and CSS exhibited a reasonable fit with predictive ability (Figure 3).

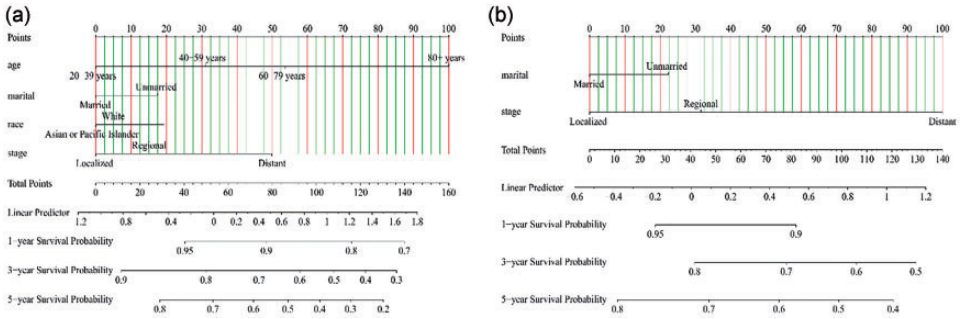


Figure 2. Nomograms predicting OS (a) and CSS (b) among patients with nasopharyngeal lymphoepithelial carcinoma.
OS, overall survival; CSS, cancer-specific survival.

Patients with LEC of the nasopharynx were grouped into high- and low-risk groups. This classification was based on the median overall score for all patients calculated from the variable scores in the OS nomogram. Using the low-risk group as a reference in the Cox regression model, the high-risk group had a 2.06-fold (95% CI = 1.59–2.67) higher risk of death. Then, we applied RMST to compare the mean survival time of the two risk groups up to a specific time. Notably, RMST could be estimated as the area under the survival curve up to the predetermined time point; therefore, we considered all survival information during this time range. In the RMST analysis, three different time points (1, 3, and 5 years) were selected to calculate the corresponding results. Of note, the average survival time of the high-risk group at specified times was significantly lower than that of the low-risk group ($P < 0.05$, Table S6).

We also compared RMST in different risk groups according to the treatment method (Figures 4 and 5). Based on the results, the effects of combined radiotherapy and chemotherapy and radiotherapy alone on RMST did not significantly differ between different risk groups at different time points. Compared with the effects of combined chemotherapy and radiotherapy, chemotherapy alone was associated with significantly worse survival.

Discussion

As a rare disease, LEC poses challenges to epidemiological research, particularly regarding the collection of a reliable number of clinical cases for exploration. To our knowledge, the case data we extracted from the SEER database represent the largest sample size of all existing studies; thus, these data were comprehensively used to explore the survival and prognostic factors of LEC.

In the present study, the median age of all patients at diagnosis was 52 years. Excluding patients with nasopharyngeal LEC (median age, 49 years), patients with different sites of disease onset were older, in line with the findings of previous studies.[14–16] Excluding LEC of the salivary glands, other sites of disease onset displayed higher incidence rates in men. Salivary gland LEC, in particular parotid gland LEC, is more common in women, and it most frequently occurs in the fourth to fifth decades of life.[17] To eliminate disparities, clarification of the impact of sex requires further research in specific cancers. The results of survival analysis demonstrated the association of advanced age with poor OS and

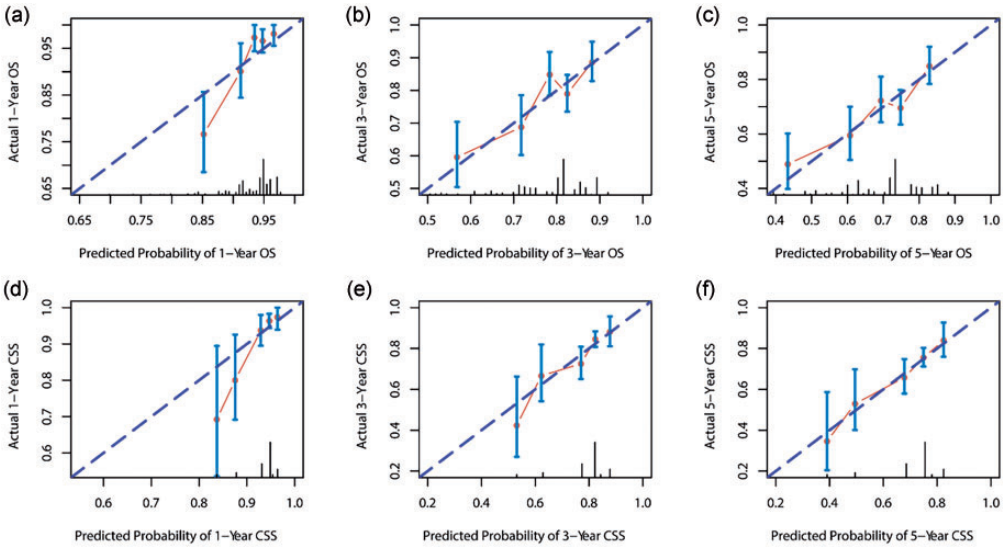


Figure 3. Calibration plots for the nomogram. (a–c) 1-, 3-, and 5-year OS and (d–f) 1-, 3-, and 5-year CSS
OS, overall survival; CSS, cancer-specific survival.

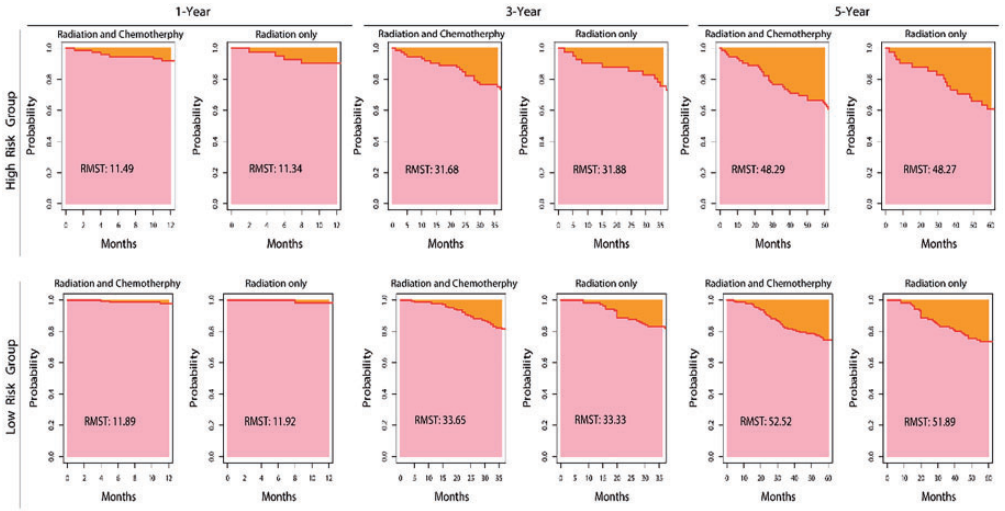


Figure 4. Comparison of the effects of combined radiotherapy and chemotherapy and radiotherapy alone on 1-, 3- and 5-year RMST among patients with nasopharyngeal lymphoepithelial carcinoma in different risk groups.
RMST, restricted mean survival time.

CSS, which might be related to their physical condition and tolerance to treatment. Patients diagnosed after 1984 had significantly better OS and CSS. By searching the literature, we found that treatment techniques have gradually changed. Originally, radiotherapy was the main treatment, and it was linked to high rates of locoregional

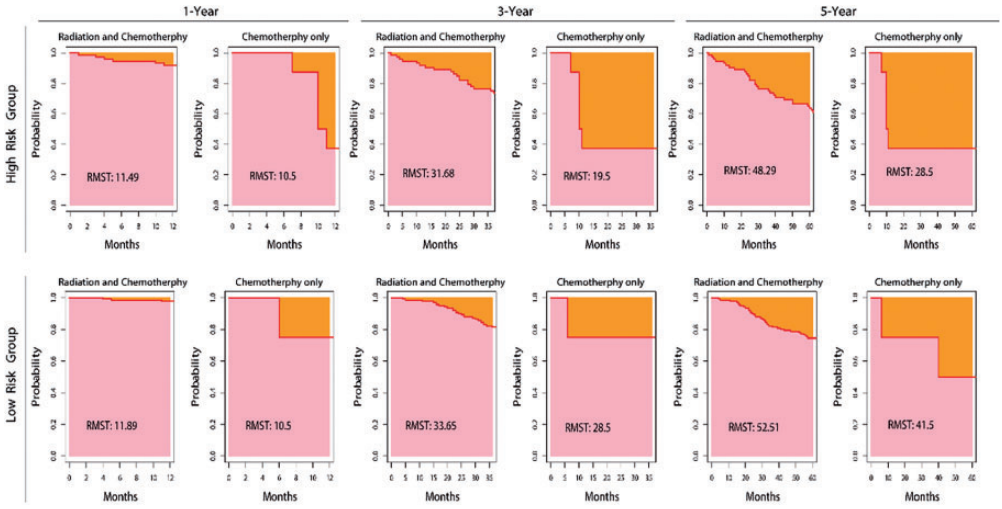


Figure 5. Comparison of the effects of combined radiotherapy and chemotherapy and chemotherapy alone on 1-, 3-, and 5-year RMST among patients with nasopharyngeal lymphoepithelial carcinoma in different risk groups.
RMST, restricted mean survival time.

tumor control. After 1985, clinical trials of radiotherapy combined with chemotherapy were gradually reported.[18–21] In the meantime, the methods of radiotherapy have been further improved, and radiation techniques have been perfected.[22,23] In addition, patient compliance and the rate of diagnosis might be additional factors. The prognosis of LEC of the larynx, glottis, and hypopharynx appears to be significantly worse, and this could have several explanations. First, diagnosis can be challenging because the tumors arise from submucosal sites, and because of the small number of cases, there is no clear reference for diagnostic criteria. Second, many patients had histologically confirmed cervical lymph node metastasis at the time of diagnosis as well as systemic metastases. Third, treatments are not standard, and the dose of radiation is still being explored. Most patients die of distant metastasis, but surgery and adjuvant chemotherapy do not effectively prevent metastasis.

Numerous studies have demonstrated racial differences in the incidence of LEC; overall, laryngeal and hypo pharyngeal LEC are more prevalent in whites than in Asians,[24] and people of Eskimo/Inuit ethnicity experience higher rates of LEC in the salivary glands.[25,26] In this study, we identified black race as a risk factor for head and neck LEC regardless of OS or CSS. The ethnic and genetic background might affect the pathogenesis of LEC, or differences in exposure factors of LEC-related etiology could arise among people in different regions.

Local spread or nodal metastases are fairly common at the time of diagnosis. Thus, establishing timely and scientific treatment management strategies is undeniably essential. Common treatment approaches include surgical resection, neck dissection, radiotherapy, chemotherapy, and combinations of several approaches. In most cases, LEC occurs in the nasal cavity, and it is morphologically similar to non-keratinizing undifferentiated nasopharyngeal carcinoma.[27] Radiotherapy is preferable because of the radiosensitivity of nasopharyngeal carcinoma.[28] This

recommendation has been validated by our findings. Non-nasopharyngeal LEC is rare, and its clinical behavior and treatment responsiveness are not fully understood. The major management strategies for laryngeal and hypopharyngeal LEC is surgery and radiotherapy.[29] For salivary LEC, it is often difficult to completely remove the tumor because of the presence of facial nerves, and thus, postoperative radiotherapy has been a significant adjuvant treatment after surgery.[30] Based on our knowledge, data on the treatment of non-nasopharyngeal LEC are limited. Overall, favorable prognoses were evident regarding the efficacy responses in clinical treatment.

Nomograms have been used in clinical prediction research.[31–33] In this study, we established nomograms to predict 1-, 3-, and 5-year OS and CSS for patients with nasopharyngeal LEC. The nomograms were validated to determine the degree of model fit and the applicability of prediction. We categorized patients into high- and low-risk groups, which allowed us to compare their corresponding treatments according to the nomogram scores. The established nomograms could accurately predict the patients' individual survival probabilities and formulate a reasonable follow-up time schedule, which significantly improved clinical practice.

This study had some limitations. First, being a retrospective study, some subjectivity is inevitable. Second, the SEER database might lack important information such as related virus detection and detailed treatment plans, which could have resulted in insufficient discussion of the relevant issues. Third, because of the rarity of the disease, the period of study enrollment was relatively large, which allowed us to better explore the survival characteristics. During this period, the staging methods and diagnosis varied over time. However, we used the SEER historical staging and year classification to partially solve this problem. Notwithstanding these shortcomings, this large population study provided valuable reference materials for this rare disease. Thus, our study is applicable to current research on LEC.

Conclusion

The present study affirmed that head and neck LEC is a rare disease, and advanced age, an unmarried status, and distant metastasis were associated with a higher risk. Compared with the effects of chemotherapy, radiotherapy has a more significant role in the treatment of LEC.

Authors' contributions

Hongtao Zhen conceived the study idea and critically revised the manuscript. Hui Deng and Jing Wei reviewed the literature, analyzed the data, and drafted the manuscript. Lihua Wu, Jianbo Song, Junping Zhang, Wenhui Yang, and Mengxian Zhang contributed to study design. All authors read and approved the final version of the manuscript as submitted and agreed to be held accountable for all aspects of the work.

Data availability statement

We analyzed publicly available data sets. These data are available in the SEER database (https://seer.cancer.gov/).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Hui Deng https://orcid.org/0000-0002-3330-3935

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