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Clinicopathological characteristics and prognosis of pulmonary large cell neuroendocrine carcinoma aged ≥ 65 years

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Abstract

Objective: The present study was designed to better characterize the clinicopathological features and prognosis in patients aged ≥ 65 years with pulmonary LCNEC.

Methods: Eligible patients with pulmonary LCNEC were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database between January 2004 and December 2013. The primary endpoints included cancer specific survival (CSS) and overall survival (OS).

Results: Data of 1,619 eligible patients with pulmonary LCNEC were collected. These patients were subsequently categorized into two groups: 890 patients in the older group (age ≥65 years), and 729 in the younger group (age < 65 years). More patients were of white ethnicity, stage I, married, and with tumor size <5 cm in the older group in comparison to the younger group. However, there were a significantly lower proportion of patients undergoing surgery, chemotherapy and radiotherapy in the older group. The 5-year CSS rates of the younger group and older group were 23.94% and 17.94% (P =0.00031), respectively, and the 5-year OS rates were 20.51% and 13.47% (P < 0.0001), respectively. Multivariate analyses indicated that older age (CSS: HR 1.20, 95%CI 1.07–1.36, P=0.0024; OS: HR 1.26, 95% CI 1.12–1.41, P<0.0001) was an independent risk factor for poor prognosis. The mortality risk of the elderly increased in almost every subgroup, especially in OS. Finally, significant predictors for better OS and CSS in patients over age 65 included tumor size <5 cm, lower stage, and receiving surgery, chemotherapy or radiotherapy.

Conclusion: The prognosis of patients aged ≥ 65 years with pulmonary LCNEC was worse than that of younger patients. However, active and effective therapy could significantly improve the survival of older patients with pulmonary LCNEC.

Introduction

Large cell neuroendocrine carcinoma (LCNEC) has been considered a rare pulmonary malignancy, accounting for only 2% to 3% of all diagnosed lung cancers (Fasano et al. 2015). LCNEC was initially categorized into the spectrum of pulmonary neuroendocrine tumors in 1991. Prior to this, it was classified as a high-grade atypical carcinoid tumor(Travis et al. 1991). Afterwards, during 1999 and 2004, the World Health Organization (WHO) admitted that LCNEC was a variant of large cell carcinoma, belonging to neuroendocrine tumors and one of the non-small cell lung cancer (NSCLC). Furthermore, pulmonary LCNEC was classified as a neuroendocrine carcinoma in combination with small cell lung cancer (SCLC), typical carcinoid, and atypical carcinoid according to the WHO 4th edition Classification of Lung Tumors(Wood et al. 2018).

Increasing life expectancy within the generalized population has resulted in a rising incidence of elderly patients with lung cancer. Additionally, roughly 47% of patients with lung cancer in the U.S. are over 70 years of age, and 14% were over 80 years (Owonikoko et al. 2007). In comparison with younger patients, older

populations diagnosed with NSCLC are commonly labeled unfit for treatment due to the increasing treatment-related toxicity. Furthermore, there were more consequential deterioration and comorbidities associated with worse life quality. Therefore, elderly patients are excluded from various studies, whose outcomes are, therefore, not suitable for the elderly(Hutchins et al. 1999; Lewis et al. 2003; Talarico et al. 2004).

Clinically, pulmonary LCNEC is thought to be an aggressive malignancy with higher risks of recurrence and metastasis in comparison with other types of NSCLC. Moreover, older patients with pulmonary LCNEC are often considered to harbor worse prognosis (Fasano et al. 2015). However, to the best of our knowledge, studies concerning the comparison between the elder group and the younger group have never been undertaken. In order to provide a better understanding of pulmonary LCNEC in the elderly for clinicians, the present study was performed and analyzed to investigate its clinicopathological characteristics, prognosis and risk factors.

Materials and Methods

Ethics statement

The SEER program has developed a comprehensive, population-based database that was established in 1973, and gets updated annually (Duggan et al. 2016). The database includes nearly 30% of United States population across multiple geographic areas (Cronin et al. 2014). The SEER Research Data Agreement was signed for accessing SEER information with the use of reference number 16462-Nov2016.We proceeded to perform research methods for obtaining information while following

approved guidelines. Data analysis from this database is considered to be non-human subjects by the Office for Human Research Protection as part of the U.S Department of Health and Human Services, because patient data was anonymized and publicly available. For these reasons no ethical approval was required.

Study population

The SEER database was used to obtain patient data (submission, November 2016). On March 6, 2018 the SEER State v8.3.5 tool was released, which was utilized for selecting and choosing eligible patients for this study. In addition, our study focused on the period between January 2004 and December 2013. The inclusion criteria were as follows: over 18 years of age at diagnosis; LCNEC was pathologically confirmed using histology (ICD-O-38013/3); restriction site recoded in ICD-O-3(International Classification of Diseases for Oncology, Third Edition)/WHO 2008 to "Lung and Bronchus". Meanwhile, the exclusion criteria included: (1) under 18 years of age; (2) multiple primary cancer diagnosis; (3) without survival data; (4) without pathological confirmation based on histology; (5) because LCNEC is a high grade neuroendocrine lung tumors, we excluded patients with low grade pathology (Grade I and Grade II); (6) without surgical method; (7) patients that did not have 6th AJCC (American Joint Committee on Cancer) staging. The patients that met these criteria were included in the SEER primary cohort.

Covariates

126 Demographic and clinical variables were extracted from the SEER database,
127 including age at diagnosis, sex, race, marital status, primary site, laterality, grade,
128 tumor size, T, N, and M stage, surgery, chemotherapy, radiotherapy, follow-up
129 information. Tumor size was a continuous variable which was transformed into a
130 categorical variable on the basis of recognized cut-off values. We used the 6th edition
131 AJCC TNM staging system, and we limited our research to between 2004 and 2013,
132 because it was published in 2004.The endpoints of this study were cancer-specific
133 survival (CSS) and overall survival (OS). CSS was defined as the interval from
134 diagnosis to the most recent follow-up date or date of death caused by pulmonary
135 LCNEC. OS was defined as the interval from diagnosis to the most recent follow-up
136 date, or date of death. Using SEER 2016, a predetermined cut-off date was decided,
137 which contained information about deaths until 2014. Therefore, the study used a
138 cut-off date of December 31, 2014.

139 *Statistical analysis*

140 Baseline continuous and categorical variables are presented as a median with
141 range and numbers with percentages, respectively. Meanwhile, clinicopathological
142 characteristics were compared with Fisher's exact tests or Pearson's $\chi 2$ as deemed
143 appropriate. Additionally, Kaplan-Meier method was utilized for estimating patient
144 survival rate. Survival differences between the groups were evaluated using the
145 log-rank tests. Univariate and multivariate COX proportional hazards regression
146 models were utilized to evaluate risk of mortality and conduct subgroup analyses.
147 Variables that were deemed to be of potential importance in univariate analysis ($P <$

0.05) or previously considered to be prognostic factors were included in multivariate analysis. All of our statistical analysis conducted used SPSS software (SPSS Inc., Chicago, USA, version 19.0). Our statistical significance level was set to $P < 0.05$.

Results

Patient screening process

A total of 1619 eligible patients with pulmonary LCNEC were included in this study. The screening process was described in Figure 1. Median age at diagnosis of all patients was 66 years (range, 18–94 years). Using median age and previous clinical studies as guides (Brueckl et al. 2018; Feliciano et al. 2018; Hutchins et al. 1999; Lembicz et al. 2018; Lewis et al. 2003), we divided the included patients into two groups based on age: younger (aged <65 years) (N= 729), and older (aged ≥65 years) (N =890) patients.

Clinicopathological characteristics

The clinicopathological features of all enrolled patients were summarized in Table 1. In the younger group, the median age was 57 years, while the median age of the older group (≥65 years) was 73 years. In the older group, more patients were white (P=0.004), married (P<0.001), of stage I (P=0.022), with tumor size <5 cm (P=0.013); while with significantly lower proportion of surgery (P<0.001), chemotherapy (P<0.001) and radiotherapy (P<0.001).

The Impact of Age on the Prognosis

Univariate analysis revealed that age at diagnosis, sex, primary site, laterality, tumor size, AJCC stage, surgery, chemotherapy and radiotherapy were associated with survival in patients with pulmonary LCNEC (Table 2). Subsequent multivariate analysis indicated that older age (≥65years) (CSS: HR 1.20, 95%CI 1.07–1.36, P=0.0024; OS: HR 1.26, 95% CI 1.12–1.41, P<0.0001) was an independent prognostic risk factor for CSS and OS (Table 3).

Survival analysis and Subgroup analysis

The 5-year CSS rates of the younger group and older group were 23.94% and 17.94% (P =0.00031), respectively, and the 5-year OS rates were 20.51% and 13.47% (P < 0.0001), respectively (Figure 2). Subgroup analysis revealed that CSS in the older group was lower than that in the younger group, consistent with the findings in the overall study population. Additionally, CSS was statistically significant in the subgroups stratified by female, AJCC stage I, tumor size <5 cm, and chemotherapy, without radiotherapy (Figures 3). Meanwhile, patients of the older group in nearly all subgroups harbored significantly lower OS, except those with primary tumor location in main bronchus, bilateral tumor, AJCC stage II, stage III and undergoing segmentectomy, pneumonectomy and radiotherapy (Figures 4).

Prognostic survival factors of older group patients

Univariate and multivariate analyses found that tumor size, AJCC stage, surgery, chemotherapy, radiotherapy were independent risk factors for prognosis in the older group (≥65years) (Table 4). Moreover, patients with tumor ≥ 5cm and advanced stage had worse prognosis. Additionally, surgery, chemotherapy and radiation significantly prolonged the survival duration of older patients.

Discussion

The incidence of pulmonary LCNEC is rare, representing only 3% of all types of diagnosed lung cancer. Thus, the published studies of pulmonary LCNEC commonly included limited patients (Brueckl et al. 2018; Carretta et al. 2000; Mazieres et al. 2002; Zacharias et al. 2003). In this study, we found that more LCNEC patients were white, married, of stage I, with tumor size <5 cm in older group; and the proportion of patients undergoing surgery, radiotherapy and chemotherapy were significantly lower. In addition, older age (≥65years) was an independent prognostic risk of survival. Moreover, tumor size, AJCC stage, surgery, chemotherapy, radiotherapy were independent prognostic risk factors for older patients.

Pulmonary LCNEC is biologically aggressive, with poor prognosis (Fasano et al. 2015). The 5-year OS rate for LCNEC after resection has been reported to range from 13 to 57% (Liang et al. 2015; Varlotto et al. 2011; Younossian et al. 2002). Similarly, in our study, we found that the 5-year OS rate in the older patient group and the younger group as 13.47% and 20.51%, respectively, which are consistent with

previous studies. Meanwhile, further subgroup analysis revealed that survival risk increased in almost all subgroups, especially in the OS.

There are limited studies assessing how age impacts prognosis due to the low incidence of pulmonary LCNEC. Kujtan and colleagues reported that patients over 70 had worse survival outcomes (Kujtan et al. 2018). Additionally, Wu et al. confirmed that age was a prognostic factor for pulmonary neuroendocrine tumors, which, however, only included 23 patients (5.7%) with pulmonary LCNEC (Wu et al. 2014). Herein, our study analyzed data from 1,619 patients diagnosed with pulmonary LCNEC, and found that those elderly patients harbored significantly worse survival outcomes.

Up to date, the standard therapeutic regimen for pulmonary LCNEC is still uncertain, especially for elderly patients. Nevertheless, it is universally accepted that primary surgery is still the first option in operable patients (Naidoo et al. 2016), which constitutes the principal way to obtain an accurate diagnosis (Fasano et al. 2015). In our research, surgery was an independent prognostic factor. The role of chemotherapy or radiotherapy in the treatment of pulmonary LCNEC also remains unclarified (Hiroshima & Mino-Kenudson 2017). Dresler et al. (Dresler et al. 1997) reported no survival benefits from postoperative chemotherapy, radiation therapy, or both in patients with resected LCNEC. Shimada et al. (Shimada et al. 2012) demonstrated that overall response rate to the initial chemotherapy or chemo-radiotherapy and the survival outcomes of high-grade neuroendocrine carcinoma (HGNEC)-probable LCNEC were comparable to those of SCLC. In our study, we found that

chemotherapy and radiotherapy were protective factors for elderly pulmonary LCNEC. However, we are still unaware of how to choose chemotherapy and chemotherapeutic regimen. Unfortunately, further analysis is not possible at present due to the inaccessible specific content of chemotherapy and radiotherapy. Nevertheless, it is necessary to cautiously choose the therapeutic regimen for elderly pulmonary LCNEC.

To our knowledge, it is the largest retrospective analysis on the prognostic effect of age in pulmonary LCNEC. Based on a large population, there were certain limitations that should be noted in our study. Firstly, as a retrospective study, we selected patients according to inclusion and exclusion criteria, which might result in potential risk of selection bias. Secondly, there were some clinicopathological parameters associated with prognosis which were unavailable in the SEER database, such as surgical margin status or the specific dosage of chemotherapy and radiotherapy. Although retrospective studies may not always have all the putative parameters available, often, as in this case, the results are certainly of great clinical value. Bridging these research gaps will be a major focus in future research.

Conclusion

In conclusion, our study found that the prognosis in patients aged ≥ 65 years with pulmonary LCNEC was worse than that of younger ones. However, active and effective therapy can significantly improve survival rates for elderly, and multidisciplinary treatment could provide more survival benefits for elderly patients.

Our findings could provide better understanding for clinicians of clinicopathological features and prognosis in patients over 65 years of age with pulmonary LCNEC.

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Figure Legends

Fig1. Flow chart for screening eligible patients.

Fig2. Kaplan–Meier survival plots for different age group patients showing (A) cancer-specific survival (CSS) and (B) overall survival (OS) (log-rank tests).

Fig3. Subgroup analysis of cancer-specific survival (CSS) between the two age groups.

Fig4. Subgroup analysis of overall survival (OS) between the two age groups.