The role of radiotherapy in pulmonary large cell neuroendocrine carcinoma: propensity score matching analysis

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ABSTRACT

The aim of the study was to investigate the survival advantage of radiotherapy (RT) in patients with pulmonary large cell neuroendocrine carcinoma (LCNEC). Patients with pulmonary LCNEC were extracted from the Surveillance, Epidemiology, and End Results (SEER) dataset between January 2004 and December 2013. Propensity score matching (PSM) analysis with 1:1 was used to ensure well-balanced characteristics of all comparison groups. A total of 1480 eligible cases were identified, with a median follow-up time of 11 months (0–131 months). After PSM, 980 patients were classified in no radiotherapy (No RT) and radiotherapy (RT) groups (n = 490 each). Patients in the RT group harbored significantly higher 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) rates compared to those in the No RT group (both \( P < 0.05 \)). Furthermore, RT was an independent favorable prognostic factor of OS as well as CSS in multivariate analysis, both before \( [OS: \text{hazard ratio (HR)} 0.840, 95\% \text{confidence interval (CI)} 0.739–0.954, P = 0.007; CSS: \text{HR} 0.847, 95\% \text{CI} 0.741–0.967, P = 0.014] \) and after \( (OS: \text{HR} 0.854, 95\% \text{CI} 0.736–0.970, P = 0.016; CSS: \text{HR} 0.848, 95\% \text{CI} 0.735–0.978, P = 0.023) \) PSM. In subgroup analysis, American Joint Committee on Cancer (AJCC) stage II and III, tumor size 5-10 cm, patients who underwent no surgery, or patients who received chemotherapy could significantly benefit from RT (all \( P < 0.05 \)). To sum up, our findings suggested that RT could prolong the survival of patients with pulmonary LCNEC, especially those with stage II and III, tumor size 5-10 cm, those with no surgery, or those who received chemotherapy.

Keywords: pulmonary large cell neuroendocrine carcinoma; radiotherapy; survival; surveillance; epidemiology, and end results (SEER)

INTRODUCTION

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is an uncommon malignancy, accounting for \( \sim 3\% \) of all lung cancers [1]. In 1991, Travis et al. suggested that the large cell neuroendocrine tumor was a new type of solitary pulmonary neuroendocrine tumor, which was different from typical, atypical carcinoid and small cell carcinoma [2]. Then, in 1999 and 2004, the World Health Organization (WHO) concluded that pulmonary LCNEC was a variant of large cell carcinoma, which was among the pulmonary neuroendocrine tumors, and belonged to non-small cell lung cancer (NSCLC) [3, 4].

Due to its low incidence and inadequate relevant clinical trial data, there is a lack of clinical understanding of the biological characteristics of pulmonary LCNEC [1, 5]. Furthermore, the role of radiotherapy (RT) in the treatment of local or advanced pulmonary LCNEC is still unclear, but some authors suggest its use in locally advanced disease setting [6, 7]. However, as far as we know, there is no large-population-based report on the role of RT in pulmonary LCNEC, and small-scale studies have yielded conflicting results [1]. Based on this, the present study aimed to investigate the survival advantage of RT in patients with pulmonary LCNEC.

MATERIALS AND METHODS

Ethics statement

The National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program, initiated from 1973 and annually updated,
utilizes population-based data to develop comprehensive sources [8], covering ~30% of the US population [9]. The SEER Data Agreement was signed for access to SEER information under reference number 16462-Nov2016. The data were obtained following strictly approved guidelines. The data, which had been obtained by the United States Department of Health and Human Services, was considered by the Office for Human Research Protection to be on non-human subjects as they were publicly available and de-identified. Thus, the study did not require approval by the institutional review board.

**Study population**

The SEER+State v8.3.5 tool, released on 6 March 2018, was used to determine and select eligible patients. The study duration ranged from January 2004 to December 2013. The inclusion criteria were as follows: age at diagnosis ≥ 20 years; LCNEC pathologically confirmed based on histology (ICD-O-3/WHO 2008 (International Classification of Diseases for Oncology, Third Edition) to 'Lung and Bronchus'). The exclusion criteria were as follows: (i) age at diagnosis ≤ 20 years; (ii) patients with >1 primary malignancy; (iii) patients with low-grade pathology (Grade I and Grade II) because LCNEC is a type of high-grade neuroendocrine lung tumor; (iv) patients without pathological diagnosis based on histology; (v) patients without prognostic data; (vi) patients without complete important clinicopathological data, including marital status, race, primary tumor site, 6th American Joint Committee on Cancer (AJCC) tumor stage and specific surgical type; (vii) patients who died within 3 months after surgery. The remainder were defined as the SEER primary cohort.

**Covariates**

The following demographic and clinicopathological data were collected from the SEER dataset: age at diagnosis, marital status, race, gender, primary location, laterality, grade, tumor size, AJCC stage, surgery, chemotherapy, RT and follow-up information. Continuous variables (age and tumor size) were converted into categorical ones based on well-defined cut-off values. We used the AJCC staging system 6th edition, and we limited our research to between 2004 and 2013, because this edition was published in 2004.

The primary endpoint was overall survival (OS), while cancer-specific survival (CSS) was the secondary endpoint. OS refers to the duration from diagnosis to the most recent follow-up date or date of death. CSS refers to the time duration from diagnosis to the most recent follow-up date or date of death caused by pulmonary LCNEC. There was a predetermined cut-off date based on the SEER 2016 submission database, containing death information until 2014. The cut-off date was 31 December 2014 in our study.

**Propensity score matching**

Selection bias might be unavoidable in observational research, leading to unevenly distributed confounding factors between two groups. Propensity score matching (PSM) is the conditional probability of assignment to a particular treatment given a vector of observed covariates [10]. Therefore, PSM was utilized in the present research to reduce selection bias and imbalanced distributions of the confounding factors [11]. In this study, PSM was performed between the RT group and the No RT group of each subgroup. Propensity scores for all patients were estimated using a logistic regression model, which included all covariates that might have affected patients survival except RT (age at diagnosis, sex, race, marital status, primary site, laterality, grade, tumor size, AJCC stage, surgery and chemotherapy). The PSM plugin of SPSS software was utilized to determine the propensity score in each case. Afterwards, PSM was performed using 1:1 nearest neighbor matching with a caliper of 0.01 for the acceptance of a matched pair.

**Statistical analyses**

Continuous data are shown as mean with standard deviation (SD) and categorical variables are presented as numbers with percentages. Pearson’s χ2 or Fisher’s exact tests were utilized to compare the clinicopathological characteristics before and after PSM. The Kaplan–Meier method was employed to determine patients’ survival rates, along with log-rank tests for assessing differences among groups. Both univariate and multivariate Cox proportional hazards regression analyses were used to examine the correlations between diverse factors and survival. To be specific, variables of potential significance in univariate analysis (P < 0.05) or previously reported to be prognostic factors were enrolled in multivariate analysis. SPSS software (SPSS Inc., Chicago, USA, version 23) was used for statistical analysis and P < 0.05 was considered as statistically significant.

**RESULTS**

**Patient characteristics before and after PSM**

In total, 1480 cases were enrolled in this research. Patients were further divided into a No RT (n = 920) and an RT (n = 560) group, and the specific screening process is shown in Fig. 1. The distribution of patient characteristics in both groups are displayed in Table 1. The median follow-up time was 11 months (0–131 months). In terms of survival rates, the 1-, 3- and 5-year OS and CSS were 47.7, 23.5 and 17.3% and 50.5, 27.0 and 21.2%, respectively. The following variables: marital status, race, sex, age, primary site, grade, laterality, tumor size, AJCC stage, surgery and chemotherapy were included in PSM. After PSM at a 1:1 ratio, both No RT and RT groups comprised 490 patients, respectively. Despite the significant differences in certain variables (age, primary site, chemotherapy), no significant differences were observed in grade (P = 0.385), tumor size (P = 0.162), AJCC stage (P = 0.635) and surgery (P = 0.420) after PSM (Table 1).

**CSS and OS after PSM**

After PSM, the 1-, 3- and 5-year OS rates were higher in the RT group compared to the No RT groups (41.2, 14.8 and 8.8% vs 30.9, 11.2 and 6.1%, respectively; P < 0.001) (Fig. 2A). Consistently, the 1-, 3- and 5-year CSS rates were significantly higher in the RT group than in the No RT group (42.9, 16.6 and 11.0% vs 33.9, 12.1 and 7.6%, respectively; P = 0.002) (Fig. 2B).

**Prognostic factors for survival before and after PSM**

Baseline characteristics as well as selected variables were enrolled in a univariate analysis between two groups for comparison of both OS and CSS (Table 2). Multivariate analysis found that patients receiving RT harbored both better OS [hazard ratio (HR) 0.840, 95% confidence
Table 1. Baseline characteristics before and after propensity score matching

| Variable                  | Before PSM | After PSM | P   | Before PSM | After PSM | P   |
|---------------------------|------------|-----------|-----|------------|-----------|-----|
| Age, years                |            |           |     |            |           |     |
| <60                       | 236 (25.65%)| 182 (32.50%)| 0.008 | 116 (23.67%)| 162 (33.06%)| <0.001 |
| ≥60 and <80               | 589 (64.02%)| 336 (60.00%)|    | 315 (64.29%)| 293 (59.80%)|    |
| ≥80                       | 95 (10.33%) | 42 (7.50%) |    | 59 (12.04%) | 35 (7.14%)  |    |
| Sex                       |            |           | 0.733 | 0.401      |           |     |
| Male                      | 516 (56.09%)| 309 (55.18%)|    | 287 (58.57%)| 274 (55.92%)|    |
| Female                    | 404 (43.91%)| 251 (44.82%)|    | 203 (41.43%)| 216 (44.08%)|    |
| Race                      |            |           | 0.795 | 0.890      |           |     |
| White                     | 773 (84.02%)| 467 (83.39%)|    | 408 (83.27%)| 410 (83.67%)|    |
| Black                     | 114 (12.39%)| 69 (12.32%) |    | 62 (12.65%) | 58 (11.84%)  |    |
| Other                     | 33 (3.59%)  | 24 (4.29%)  |    | 20 (4.08%)  | 22 (4.49%)  |    |
| Marital status            |            |           | 0.306 | 0.063      |           |     |
| Married                   | 494 (53.70%)| 316 (56.43%)|    | 249 (50.82%)| 278 (56.73%)|    |
| Unmarried                 | 426 (46.30%)| 244 (43.57%)|    | 241 (49.18%)| 212 (43.27%)|    |
| Primary site              |            |           | 0.102 | 0.015      |           |     |
| Main bronchus             | 36 (3.91%)  | 26 (4.64%)  |    | 24 (4.90%)  | 26 (5.31%)  |    |
| Upper lobe                | 550 (59.78%)| 368 (65.71%)|    | 276 (56.33%)| 325 (66.33%)|    |
| Middle lobe               | 56 (6.09%)  | 26 (4.64%)  |    | 31 (6.33%)  | 22 (4.49%)  |    |
| Lower lobe                | 262 (28.48%)| 129 (23.04%)|    | 147 (30.00%)| 106 (21.63%)|    |
| Overlapping lesion        | 16 (1.74%)  | 11 (1.96%)  |    | 12 (2.45%)  | 11 (2.24%)  |    |
| Grade                     |            |           | <0.001 | 0.385      |           |     |
| Poorly differentiated     | 389 (42.28%)| 177 (31.61%)|    | 161 (32.86%)| 151 (30.82%)|    |
| Undifferentiated          | 126 (13.70%)| 58 (10.36%) |    | 63 (12.86%) | 53 (10.82%)  |    |
| Unknown                   | 405 (44.02%)| 325 (58.04%)|    | 266 (54.29%)| 286 (58.37%)|    |
| Laterality                |            |           | 0.655 | 0.174      |           |     |
| Bilateral                 | 2 (0.22%)  | 0 (0.00%)  |    | 2 (0.41%)  | 0 (0.00%)  |    |
| Left                      | 373 (40.54%)| 233 (41.61%)|    | 216 (44.08%)| 198 (40.41%)|    |
| Right                     | 545 (59.24%)| 327 (58.39%)|    | 272 (55.51%)| 292 (59.59%)|    |
| Tumor size                |            |           | <0.001 | 0.162      |           |     |
| <2 cm                     | 181 (19.67%)| 66 (11.79%) |    | 59 (12.04%) | 53 (10.82%)  |    |
| ≥2 cm and <5 cm           | 436 (47.39%)| 231 (41.25%)|    | 219 (44.69%)| 203 (41.43%)|    |
| ≥5 cm and <10 cm          | 173 (18.80%)| 161 (28.75%)|    | 118 (24.08%)| 141 (28.78%)|    |
| ≥10 cm                    | 34 (3.70%)  | 42 (7.50%)  |    | 29 (5.92%)  | 40 (8.16%)  |    |
| Unknown                   | 96 (10.43%) | 60 (10.71%) |    | 65 (13.27%) | 53 (10.82%)  |    |
| AJCC stage                |            |           | <0.001 | 0.635      |           |     |
| IA                        | 184 (20.00%)| 17 (3.04%)  |    | 19 (3.88%)  | 17 (3.47%)  |    |
| IB                        | 162 (17.61%)| 29 (5.18%)  |    | 26 (5.31%)  | 29 (5.92%)  |    |
| IIA                       | 23 (2.50%)  | 5 (0.89%)  |    | 6 (1.22%)  | 5 (1.02%)  |    |
| IIB                       | 51 (5.54%)  | 22 (3.93%)  |    | 29 (5.92%)  | 21 (4.29%)  |    |
| IIIA                      | 56 (6.09%)  | 85 (15.18%) |    | 44 (8.98%)  | 58 (11.84%) |    |
| IIIB                      | 84 (9.13%)  | 81 (14.46%) |    | 75 (15.31%) | 65 (13.27%) |    |
| IV                        | 360 (39.13%)| 321 (57.32%)|    | 291 (59.39%)| 295 (59.02%)|    |
| Surgery                   |            |           | <0.001 | 0.420      |           |     |
| No surgery                | 446 (48.48%)| 455 (81.25%)|    | 372 (75.92%)| 387 (78.98%)|    |
| Segmentectomy/wedge resection | 91 (9.89%) | 29 (5.18%) |    | 39 (7.96%)  | 28 (5.71%)  |    |
| Lobectomy/bilobectomy     | 342 (37.17%)| 61 (10.89%) |    | 67 (13.67%) | 60 (12.24%) |    |
| Pneumonectomy             | 41 (4.46%)  | 15 (2.68%)  |    | 12 (2.45%)  | 15 (3.06%)  |    |
| Chemotherapy              |            |           | <0.001 | <0.001     |           |     |
| No/unknown                | 544 (59.13%)| 151 (26.96%)|    | 232 (47.35%)| 145 (29.59%)|    |
| Yes                       | 376 (40.87%)| 409 (73.04%)|    | 258 (52.65%)| 345 (70.41%)|    |
Subgroup analysis for OS and CSS after PSM

Subgroup analysis of OS and CSS demonstrated that most study populations could benefit from RT with regard to survival (Figs 3 and 4). AJCC stage II and III, tumor size 5–10 cm, no surgery or received
Table 2. Univariate analyses for prognostic factors before PSM

| Variable     | OS HR (95% CI) | P-Value | OS HR (95% CI) | P-Value |
|--------------|----------------|---------|----------------|---------|
| Sex          |                |         |                |         |
| Male         | 1.0            |         | 1.0            |         |
| Female       | 0.823 (0.733, 0.924) | <0.001  | 0.840 (0.744, 0.948) | 0.005  |
| Race         |                |         |                |         |
| White        | 1.0            |         | 1.0            |         |
| Black        | 1.072 (0.903, 1.273) | 0.427  | 1.077 (0.900, 1.289) | 0.419  |
| Other        | 0.985 (0.735, 1.320) | 0.919  | 0.949 (0.694, 1.298) | 0.743  |
| Marital status |            |         |                |         |
| Married      | 1.0            |         | 1.0            |         |
| Unmarried    | 1.065 (0.950, 1.194) | 0.281  | 1.032 (0.915, 1.165) | 0.604  |
| Age, years   |                |         |                |         |
| <60          | 1.0            |         | 1.0            |         |
| ≥60 and <80  | 1.262 (1.105, 1.441) | <0.001  | 1.214 (1.057, 1.394) | 0.006  |
| ≥80          | 1.990 (1.615, 2.451) | <0.001  | 1.851 (1.484, 2.309) | <0.001 |
| Primary site |                |         |                |         |
| Main bronchus | 1.0            |         | 1.0            |         |
| Upper lobe   | 0.474 (0.361, 0.621) | <0.001  | 0.475 (0.358, 0.631) | <0.001 |
| Middle lobe  | 0.639 (0.453, 0.901) | 0.011  | 0.651 (0.455, 0.933) | 0.019  |
| Lower lobe   | 0.512 (0.385, 0.679) | <0.001  | 0.514 (0.382, 0.692) | <0.001 |
| Overlapping lesion | 0.617 (0.374, 1.018) | 0.059  | 0.616 (0.364, 1.043) | 0.071  |
| Grade        |                |         |                |         |
| Poorly differentiated | 1.0 |         | 1.0            |         |
| Undifferentiated | 1.120 (0.923, 1.358) | 0.250  | 1.129 (0.920, 1.386) | 0.244  |
| Unknown      | 1.772 (1.564, 2.008) | <0.001  | 1.833 (1.606, 2.091) | <0.001 |
| Laterality   |                |         |                |         |
| Bilateral    | 1.0            |         | -              |         |
| Left         | 1.829 (0.257, 13.017) | 0.547  | -              |         |
| Right        | 1.973 (0.277, 14.034) | 0.497  | -              |         |
| Tumor size   |                |         |                |         |
| <2 cm        | 1.0            |         | 1.0            |         |
| ≥2 cm and <5 cm | 1.603 (1.340, 1.918) | <0.001  | 1.623 (1.339, 1.968) | <0.001 |
| ≥5 cm and <10 cm | 2.430 (1.998, 2.955) | <0.001  | 2.563 (2.082, 3.155) | <0.001 |
| ≥10 cm       | 3.465 (2.604, 4.610) | <0.001  | 3.874 (2.888, 5.197) | <0.001 |
| Unknown      | 3.882 (3.091, 4.875) | <0.001  | 4.236 (3.337, 5.377) | <0.001 |
| AJCC stage   |                |         |                |         |
| IA           | 1.0            |         | 1.0            |         |
| IB           | 1.138 (0.861, 1.502) | 0.364  | 1.296 (0.944, 1.778) | 0.109  |
| IIA          | 1.569 (0.925, 2.661) | 0.094  | 1.994 (1.143, 3.478) | 0.015  |
| IIB          | 2.345 (1.687, 3.261) | <0.001  | 2.786 (1.933, 4.014) | <0.001 |
| IIIA         | 2.309 (1.763, 3.024) | <0.001  | 2.909 (2.154, 3.929) | <0.001 |
| IIIB         | 3.769 (2.918, 4.869) | <0.001  | 4.460 (3.339, 5.957) | <0.001 |
| IV           | 6.918 (5.566, 8.597) | <0.001  | 8.778 (6.839, 11.266) | <0.001 |
| Surgery      |                |         |                |         |
| No surgery   | 1.0            |         | 1.0            |         |
| Segmentectomy/wedge resection | 0.328 (0.262, 0.411) | <0.001  | 0.298 (0.233, 0.380) | <0.001 |
| Lobectomy/bilobectomy | 0.200 (0.171, 0.234) | <0.001  | 0.176 (0.148, 0.209) | <0.001 |
| Pneumonectomy | 0.316 (0.229, 0.434) | <0.001  | 0.290 (0.205, 0.410) | <0.001 |
| Chemotherapy |                |         |                |         |
| No/unknown   | 1.0            |         | 1.0            |         |
| Yes          | 1.010 (0.900, 1.133) | 0.870  | 1.074 (0.951, 1.213) | 0.247  |
Table 3. Multivariate analyses with or without RT in patients before and after PSM; model adjusted for age, gender, race, marital status, primary site, grade, laterality, tumor size, AJCC stage, surgery and chemotherapy.

| Variable   | Before PSM | After PSM |
|------------|------------|-----------|
|            | HR (95% CI) | P-Value   | HR (95% CI) | P-Value   |
| OS         |            |           |            |
| No RT      | 1.0        |           | 1.0        |           |
| RT         | 0.840 (0.739, 0.954) | 0.007 | 0.854 (0.736, 0.970) | 0.016 |
| CSS        |            |           |            |
| No RT      | 1.0        |           | 1.0        |           |
| RT         | 0.847 (0.741, 0.967) | 0.014 | 0.848 (0.735, 0.978) | 0.023 |

Fig. 3. Forest plot of subgroup analysis for OS after 1:1 PSM.

chemotherapy patients could significantly benefit from RT in terms of OS and CSS (all \( P < 0.05 \)).

**DISCUSSION**

To our knowledge, this is the first large-population-based study to investigate the role of RT in treating pulmonary LCNEC by using PSM. Consequently, after performing both multivariate regression and PSM analyses, we demonstrated that RT could provide significant survival benefit for patients with pulmonary LCNEC, especially for those with stage II and III.

Pulmonary LCNEC is biologically aggressive with poor prognosis [12]. The 5-year OS in patients receiving resection of LCNEC has been demonstrated to vary from 13 to 57% [4, 13, 14]. Our study found that the 5-year CSS and OS rates of pulmonary LCNEC were 21.2 and 17.3%, respectively. This was a lower survival rate compared to those in previous studies, possibly due to the fact that most of the population included were in stage IV (\( n = 681, 46.0\% \)).
Fig. 4. Forest plot of subgroup analysis for CSS after 1:1 PSM.

The role of RT in localized or advanced pulmonary LCNEC treatment remains undefined [15–17]. Dresler et al. [18] demonstrated that patients with resected LCNEC failed to gain survival benefit from postoperative chemotherapy, RT or both. In contrast, Shimada et al. [19] reported comparable outcomes of overall response rate to initial chemotherapy or chemo-RT as well as survival outcomes between high-grade neuroendocrine carcinoma (probable LCNEC) and SCLC. In this study, we found that RT is a significantly protective factor for pulmonary LCNEC. In addition, RT for patients with stage II and III pulmonary LCNEC can significantly improve the survival rate. Moreover, patients with tumor size 5–10 cm, no surgery, or who received chemotherapy could also benefit significantly from RT.

There are certain limitations to this study. Firstly, as in all observational research, it is almost impossible to avoid bias. Although the PSM method could attenuate the bias resulting from unevenly distributed measured covariates, the bias originating from unmeasured ones is unavoidable. Secondly, although 12 variables were involved, there are still some variables that SEER does not include, such as the chemotherapy regimen, surgical margin status and vascular invasion. Thirdly, the definition of RT in the SEER dataset is RT administration during the first course of cancer-directed therapy, without data concerning dose or intended target. Therefore, we had no information about the radiation dose timing, intent, methods, side effects and second-line chemotherapy, which may all have contributed to study bias. Instead of showing it in detail, we aimed to illustrate the general survival advantage of RT in pulmonary LCNEC patients. Thus, the currently accessible information in the SEER dataset could readily satisfy our study requirements. In other words, we had no intention of examining the specific types, dose, timing, intent or methods of RT in pulmonary LCNEC. Nevertheless, the study population was extracted from a national dataset, which could decrease the potential selection bias to some extent. As both multivariable and PSM analyses were performed, while both CSS and OS results did not alter significantly, the findings should be valid and stable.

CONCLUSION
Our findings based on the SEER database support that RT could provide survival benefit in patients with pulmonary LCNEC, especially for those with stage II and III, tumor size 5-10 cm, with no surgery or who received chemotherapy.

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CONFLICT OF INTEREST
None declared.

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