INTRODUCTION

Neuroendocrine tumors of the lungs are a clearly different group of tumors with definite ultrastructural, immunohistochemical, and molecular features [1]. Pulmonary neuroendocrine tumors include the following four tumor subtypes: low grade typical carcinoid tumor, intermediate grade atypical carcinoid tumor, high grade large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung carcinoma (SCLC) [2]. Most of these tumors are formed from SCLC and constitute approximately 25% of all primary pulmonary carcinomas. LCNEC is rare and its incidence varies between 2.1 and 3.5% [3, 4]. It was first described by Travis et al. in 1991 as a tumor with a large cell morphology with a low nuclear-to-cytoplasmic ratio, a high mitotic activity (>10 mitoses per 10 high-power fields [HPF]), dense necrosis, along with neuroendocrine differentiation (by immunohistochemistry or electron microscopy) [5]. These features were accepted by World Health Organization (WHO) as diagnostic criteria, in 1999.

Although the original World Health Organization (WHO-2004) classification categorized LCNEC as a variant of large cell carcinomas in the lung neuroendocrine tumor group, WHO-2015 currently classifies LCNEC as a group of neuroendocrine neoplasms with SCLC, TCT, and ACT [2, 6]. While LCNEC has a poorer prognosis compared to both NSCLC and large cell carcinomas without neuroendocrine differentiation, it is relatively similar to that of SCLC. Studies suggest that LCNECs are ideally treated like SCLCs [7, 8]. However, LCNECs are substantially less chemo-responsive to platinum/etoposide regimen [9]. Additionally, LCNEC prognosis is heterogeneous, without any no proven treatment modality. Considering this, we aimed to evaluate the clinicopathologic features, diagnosis, and treatment of our patients with large cell neuroendocrine carcinoma of the lung, to contribute to the literature.
MATERIALS and METHODS

Patients
We retrospectively collected the data of 62 patients who were histopathologically diagnosed with lung LCNEC in the Hospital between January 2010 and January 2016. Patient age, gender, laboratory parameters, diagnostic pattern, tumor characteristics, staging, tumor localization, treatment including surgery, radiation and systemic therapy, chemotherapy regimen, immunohistochemistry features, and mortality were recorded.

Seventh version of International Association for the Study of Lung Cancer (TNM) was used for staging the tumor, node, metastasis [10]. Follow-up evaluations included physical examination, serum biochemistry, complete blood cell counts, CT scans of thorax, and other imaging examinations if indicated. Clinical and imaging examinations were performed at an interval of 3 months for the first year. The patients were examined every 6 months for the following 2 years and annually thereafter. Disease progression was determined by considering the radiologic or histologic examination. The overall survival was calculated (OS) starting from the beginning of treatment to the time of death or last follow-up. Progression-free survival (PFS) was defined as the time from the beginning of treatment to the time of tumor progression or the last follow-up. Formal retrospective Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessment was performed for all patients with available diagnostic imaging for radiological response evaluation [11]. ORR could not be calculated in patients with available radiologic imaging, suitable for assessment by RECIST 1.1.

Pathology
Pathological diagnosis of LCNEC was established according to the 2015 WHO classification. Diagnostic criteria were large cell size, necrosis, low nuclear/cytoplasm ratio, presence of neuroendocrine morphology (palisading, organoid nesting, trabeculae, and/or rosettes), high mitotic rate, defined as >10 mitoses per 10 high-power fields (HPF) and immunohistochemical expression of at least one neuroendocrine marker such as chromogranin-A, synaptophysin, CD56/NCAM (neural cell adhesion molecule) [6]. The Ki-67 labeling index was used as an indicator of high-grade malignancy.

Non-small-cell cytomorphological features (abundant cytoplasm, prominent nucleoli and/or vesicular chromatin) was used to differentially diagnose LCNEC and SCLC. We also excluded squamous cell carcinomas by positive thyroid transcription factor-1 (TTF-1), p63, and cytokeratin 5/6. We excluded adenocarcinomas by positive periodic acid-Schiff and Alcian blue staining.

Statistical Analyses
All analyses were conducted using the Statistical Package for the Social Sciences 17.0 (SPSS Inc.; Chicago, IL, USA) statistical software. Categorical variables were described by frequencies and percentages, while the numerical variables were presented as either means and standard deviations or medians and minimum-maximum values. Kaplan Meier Analyses were conducted to calculate median survival times of the compared factors. Multivariate COX regression analysis was applied to calculate HR values. P<0.05 indicated statistical significance.

Ethical Consideration
The study was conducted according to good clinical practice and the Declaration of Helsinki and was approved by the ethics committee of Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital. Due to the retrospective design of the study, written informed consent could not be obtained from the participants.

RESULTS
Among the 13,088 patients diagnosed with lung cancer, 62 were LCNEC patients between January 2010 and January 2016. Their average age was 60.3±8.6 and were predominantly (95%) men (men/women= 59/3). Diagnosis was made through fine-needle aspiration biopsy (NAB) in 7 patients, bronchoscopy transbronchial biopsy (TBB) in 13, and surgery in 42. The tumor typically localized in the right upper lobe (43.5%). Additionally, the tumors for 46.8% of all patients were identified in peripheral locations. Tumor stage, location, and localization are summarized in Table 1. Sixteen patients presented with stage 1, 17 with stage 2, 15 with stage 3, and 14 with stage 4. Fourteen patients (22.6%) had distant metastasis at the time of diagnosis, with the following metastatic sites: liver (n=8), bone (n=6), brain (n=4), adrenal gland (n=2), and lung (n=2). Forty-two patients at clinical TNM Stage I, II or IIIA were surgically resected, two patients were declared inoperable. Most patients underwent lobectomy (n=34, 81%) and followed by pneumonectomy (n=7, 16.7%), respectively. Thirty-four patients (54.8%) received systemic chemotherapy (60% cisplatin etoposide, 15% carboplatin etoposide, 25% platinum-based combined chemotherapy including gemcitabine or vinorelbine). Nine of the operated patients were diagnosed as NSCLC by transbronchial fine needle aspiration biopsy or transthoracic fine needle aspiration biopsy before surgery so they operated accordingly. After operation pathological specimens revealed that these patients were LCNEC. Disease progression was

**MAIN POINTS**

- Neuroendocrine tumors of the lungs are a different group of tumors with definite ultrastructural, immunohistochemical, and molecular features.
- LCNEC has a poorer prognosis compared to both NSCLC and large cell carcinomas without neuroendocrine differentiation, it is relatively similar to that of SCLC.
- In this study the tumor was peripherally located in 46.8% of the patients, and we reported that most of our patients were treated with a platinum-based regimen (SCLC-based), while a small number of our patients were treated with non-SCLC-based regimens.
- In the present study, the median PFS was 29 (95% CI, 5.2-52.8 months) and median overall survival was 20 (95% CI, 3.1-36.9 months)
- Overall survival was significantly better in patients with low N, M0, low stage, and peripheral location in the entire cohort; however, overall survival was significantly poorer in patients who demonstrated disease progression requiring palliative radiotherapy.
observed in 32 patients, of which 16 were treated after the condition progressed, 5 received second line chemotherapy, 8 received palliative radiotherapy, and 3 patients received chemoradiotherapy.

CD56 in 55 patients, synaptophysin in 37 patients, chromogranin in 13 patients, p63 in 10 patients, CK5-6 in 4 patients, CK7 in 41 patients, TTF-1 in 25 patients, NE in 5 patients, were positive, respectively. Progression-free survival was significantly poorer in cases that were negative for p63 and TTF-1 (p=0.017 and 0.042, respectively) (Figure 1).

Median progression-free survival (PFS) was 29 months (SE: 12.2) (95% CI, 5.2–52.8 months) (Table 2). Progression-free survival (PFS) was significantly better in patients with low N, M0, low stage, p63 positive, and TTF-1 positive throughout the cohort (Figure 2). But progression-free survival (PFS) was significantly poorer in patients with chemotherapy combined with progression-associated palliative radiotherapy. Median overall survival (OS) was 20 months (SE: 8.6) (95% CI, 3.1–36.9 months) (Table 3). Overall survival (OS) was significantly better in patients with low N, M0, low stage, and peripheral location in the entire cohort; however, overall survival (OS) was signifi-

| Table 1. Tumor stage, location, and localization in patients with large-cell neuroendocrine carcinoma of the lung |
| --- |
| **Age (mean±SD)** | 60.3±8.6 |
| **Gender (n, %)** |  |
| Male | 59 (95.2) |
| Female | 3 (4.8) |
| **Diagnostic pattern (n, %)** |  |
| NAB | 7 (11.2) |
| TBB | 13 (21) |
| Surgery | 42 (67.8) |
| **T (n, %)** |  |
| T1 | 14 (22.5) |
| T2 | 29 (46.8) |
| T3 | 7 (11.3) |
| T4 | 12 (19.4) |
| **N (n, %)** |  |
| N0 | 31 (50) |
| N1 | 9 (14.6) |
| N2 | 11 (17.7) |
| N3 | 11 (17.7) |
| **Metastasis (n, %)** |  |
| M0 | 48 (77.4) |
| M1 | 14 (22.6) |
| **Stage (n, %)** |  |
| 1A | 8 (13) |
| 1B | 8 (13) |
| 2A | 11 (17.7) |
| 2B | 6 (9.6) |
| 3A | 11 (17.7) |
| 3B | 4 (6.5) |
| 4 | 14 (22.5) |
| **Tumor localization (n, %)** |  |
| right upper lobe | 27 (43.5) |
| Left upper lobe | 15 (24.2) |
| middle lobe | 4 (6.5) |
| right lower lobe | 6 (9.7) |
| left lower lobe | 10 (16.1) |
| **location (n, %)** |  |
| Peripheral | 29 (46.8) |
| Central | 33 (53.2) |
| **Chemotherapy (n, %)** |  |
| - | 28 (45.2) |
| + | 34 (54.8) |
| **Chemotherapy regimen (n, %)** |  |
| carboplatin etoposide | 5 (15.2) |
| cisplatin etoposide | 20 (60.6) |
| other regimens | 9 (24.2) |
| **Radiotherapy (n, %)** |  |
| - | 42 (68) |
| + | 20 (32) |
| **Surgery (n, %)** |  |
| Lobectomy | 34 (54) |
| Pneumonectomy | 7 (11.7) |
| Segmentectomy | 1 (2.3) |
| **Progression (n, %)** |  |
| - | 26 (44.8) |
| + | 32 (55.2) |
| **Post-progression therapy (n, %)** |  |
| - | 16 (50) |
| + | 16 (50) |
| **Time to progression (month) (median, IQR)** | 14 (45.5) |
| **Duration of follow-up (month) (median, IQR)** | 21.5 (44) |
| **Status (n, %)** |  |
| Living | 24 (39) |
| Ex | 38 (61) |
### Table 2. Progression-free survival

| Diagnostic pattern | Median (SE) | %95 CI | p    |
|--------------------|-------------|--------|------|
| NAB                | 5 (6.1)     | 0-17.0 | <0.001 |
| TBB                | 6 (1.6)     | 2.9-9.1 |      |
| Surgery            | -           | -      |      |
| T                  |             |        |      |
| T1                 | -           | -      | 0.195 |
| T2                 | 14 (11.2)   | 0-36.0 |      |
| T3                 | 25 (23)     | 0-70.1 |      |
| T4                 | 10 (16.2)   | 0-41.8 |      |
| N                  |             |        |      |
| N0                 | -           | -      | <0.001 |
| N1                 | 20 (7.9)    | 4.6-35.4 |      |
| N2                 | 5 (1.5)     | 2.1-7.9 |      |
| N3                 | 3 (2.4)     | 0-7.6  |      |
| M                  |             |        |      |
| M0                 | 53 (-)      | -      | <0.001 |
| M1                 | 3 (2.7)     | 0-8.4  |      |
| Stage              |             |        |      |
| I                  | -           | -      | <0.001 |
| II                 | 39 (12.6)   | 14.3-63.7 |      |
| III                | 8 (3.2)     | 1.7-14.3 |      |
| IV                 | 3 (2.7)     | 0-8.4  |      |
| Location           |             |        |      |
| Peripheral         | 53 (-)      | -      | 0.143 |
| Central            | 14 (10.7)   | 0-34.9 |      |
| Chemotherapy       |             |        |      |
| -                  | -           | -      | 0.046 |
| +                  | 10 (4.9)    | 0.3-19.7 |      |
| Chemotherapy regimen |             |        |      |
| carboplatin etoposide | 6 (3.3) | 0-12.4 | 0.205 |
| cisplatin etoposide | 7 (1.1)    | 4.8-9.2 |      |
| other              | -           | -      |      |
| Radiotherapy       |             |        |      |
| -                  | -           | -      | <0.001 |
| +                  | 6 (1.3)     | 3.4-8.6 |      |
| Surgery            |             |        |      |
| Lobectomy          | 53 (-)      | -      | 0.242 |
| Pneumonectomy      | -           | -      |      |
| P 63               |             |        |      |
| -                  | 20 (10.5)   | 0-40.5 | 0.017 |
| +                  | -           | -      |      |
| TTF-1              |             |        |      |
| -                  | 20 (11.8)   | 0-43.1 | 0.042 |
| +                  | -           | -      |      |

### Table 3. Overall Survival

| Diagnostic pattern | Median (SE) | %95 CI | p    |
|--------------------|-------------|--------|------|
| NAB                | 7 (3.7)     | 0-14.2 | <0.001 |
| TBB                | 2 (2.4)     | 0-6.7  |      |
| Surgery            | -           | -      |      |
| T                  |             |        |      |
| T1                 | -           | -      | 0.280 |
| T2                 | 20 (4.2)    | 11.7-28.3 |      |
| T3                 | 8 (12.2)    | 0-32.0 |      |
| T4                 | 12 (6.9)    | 0-25.6 |      |
| N                  |             |        |      |
| N0                 | -           | -      | <0.001 |
| N1                 | 23 (4.5)    | 14.2-31.8 |      |
| N2                 | 8 (1.6)     | 4.9-11.1 |      |
| N3                 | 4 (1.5)     | 0.9-7.0 |      |
| M                  |             |        |      |
| M0                 | 59 (23.1)   | 13.7-104 | <0.001 |
| M1                 | 4 (1.8)     | 0.6-7.4 |      |
| Stage              |             |        |      |
| I                  | -           | -      | <0.001 |
| II                 | 46 (10.4)   | 25.7-66.3 |      |
| III                | 12 (4.8)    | 2.5-21.5 |      |
| IV                 | 4 (1.6)     | 0.6-7.4 |      |
| Location           |             |        |      |
| Peripheral         | -           | -      | 0.042 |
| Central            | 20 (4.7)    | 10.8-29.2 |      |
| Chemotherapy       |             |        |      |
| -                  | 27 (18.4)   | 0-63   | 0.842 |
| +                  | 20 (3.6)    | 12.9-27.1 |      |
| Chemotherapy regimen |             |        |      |
| carboplatin etoposide | 10 (5.5) | 0-20.7 | 0.557 |
| cisplatin etoposide | 18 (6)     | 6.3-29.7 |      |
| other              | 59 (29.6)   | 1.0-117 |      |
| Radiotherapy       |             |        |      |
| -                  | 59 (-)      | -      | 0.001 |
| +                  | 10 (2.2)    | 5.8-14.2 |      |
| P 63               |             |        |      |
| -                  | 20 (5.4)    | 9.4-30.6 | 0.215 |
| +                  | -           | -      |      |
| TTF-1              |             |        |      |
| -                  | 20 (9.6)    | 1.3-38.7 | 0.219 |
| +                  | -           | -      |      |
| Progression (n, %) |             |        | <0.001 |
| -                  | -           | -      |      |
| +                  | 12 (5.6)    | 0.9-23.1 |      |
| OS                 | 20 (8.6)    | 3.1-36.9 |      |
regimens for LCNEC patients. Here, we reported that most of
regarding the use of either SCLC-based or non-SCLC-based
currently classified as non-SCLC. Therefore, there is a dilemma
similar to those of SCLC, despite the fact that LCNEC is cur-
clinical and biological characteristics of LCNEC are
46.8% of the patients.
[12]. In our study, the tumor was peripherally located in
fact that they are often peripherally- or midzone-located
literature, most LCNECs have been postoperatively diag-
formed via surgery (42/62) in our cohort of patients. In the
graphics in this disease. The diagnoses were mainly per-
Our cohort also predominantly included men (men/wom-
comes of this cohort.
In this study, we report a large number of patients with
LCNECs of the lung. We analyzed its incidence using our
lung cancer patient database, and acquired the data associ-
ated with the disease stages, clinico-pathologic features, rates
of surgery, responses to first-line therapy, and survival out-
comes of this cohort.

LCNECs are primarily observed in men (M:F=17:1) [12].
Our cohort also predominantly included men (men/women= 59/3), which was consistent with the known demo-
graphics in this disease. The diagnoses were mainly per-
formed via surgery (42/62) in our cohort of patients. In the
literature, most LCNECs have been postoperatively diag-
nosed through surgical specimens [13, 14], along with the
fact that they are often peripherally- or midzone-located
[12]. In our study, the tumor was peripherally located in
46.8% of the patients.

The clinical and biological characteristics of LCNEC are
similar to those of SCLC, despite the fact that LCNEC is cur-
tently classified as non-SCLC. Therefore, there is a dilemma
regarding the use of either SCLC-based or non-SCLC-based
regimens for LCNEC patients. Here, we reported that most of
our patients were treated with a platinum-based regimen
(SCLC-based), while a small number of our patients were
treated with non-SCLC-based regimens.

In the relevant literature, the response rate of platinum-
based chemotherapy to treat LCNEC was 60%, while that of
non-platinum-based chemotherapy remained 11% [15].
Moreover, the aforementioned study presented whether
advanced LCNEC should be treated similarly to SCLC than
non-SCLC, with respect to chemotherapeutic regimens. In
this study, the authors concluded that advanced LCNEC
could be treated appropriately in a manner similar to SCLC
rather than NSCLC. In our study, 34 patients (54.8%) received systemic chemotherapy (60% cisplatin-etoposide,
15% carboplatin etoposide, 25% platinum-based combined
chemotherapy including gemcitabine or vinorelbine), spe-
cifically with regard to the adjuvant setting. Only one
patient received neoadjuvant chemotherapy. A certain pro-
gression was observed in 32 patients, of which 16 were
treated after the progression. Five patients received second-
line chemotherapy. We were unfortunately unable to calcu-
late the response rates due to the availability of radiological
imaging.

LCNEC patients had poor prognoses. Current 5-year survival
rate in pathological stage I cases is 27-67% and average
5-year survival rate is 15-57% [3, 17]. Iyoda et al. compared
the 5-year survival rate of patients with pathological stage IA
LCNEC with patients at the same stage with adenocarcinomas
or squamous cell carcinomas of the lung and observed that
54.5% versus 89.3% respectively [18]. In the present study,
the median PFS was 29 (95% CI, 5.2-52.8 months) and
median overall survival was 20 (95% CI, 3.1-36.9 months).
We aim to report the 5-year survival of this cohort in the near future.

In the literature relevant to patients with non-squamous non-
small cell lung cancer, TTF-1 expression was independently
associated with overall survival and progression-free
survival. TTF-1 is mainly used to exclude the diagnosis of
LCNEC tumors; however, in our study TTF-1 expression
was correlated with a better PFS. There was no difference in
terms of OS, possibly due to the heterogeneity of the tumor
morphology. Furthermore, PFS and OS were correlated with
the expected stages of the tumor.

This study has several limitations. First, this is a single-center
retrospective database study; therefore, the patients in this
study come from a specific region and may not represent
the whole population. Certain clinical characteristics may
not have been recorded due to the retrospective design
of the study. Moreover, due to the rarity of this tumor, the
number of participants in the study was low for subgroup
divisions, thus for some comparisons the number of patients
in each group did not reach the level required for statistical
significance.

In conclusion, our study demonstrates clinic, pathologic
factors, and survival outcomes of LCNEC patients, which is
a rare group of thoracic malignancies. We believe that it is
important to conduct prospective randomized trials in the
future with a larger population.
**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013) and was approved by the scientific committee of Dr Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (No: 49109414-806.02.02).

**Informed Consent:** Due to the retrospective design of the study, informed consent was not taken.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - A. K. Ç.; Design - K. C. C.; Supervision - E. Y., B. K.; Resource - G. K., G. V. Ş.; Materials - Z. Ö.; Data Collection and/or Processing - A. A., S. T., G. B.; Analysis and/or Interpretation - Y. V.; Literature Search - A. M., Z. A.; Writing - Y. V., G. K.; Critical Reviews - G. B., Y. V.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**REFERENCES**

1. Iyoda A, Travis W, Sarkaria IS, et al. Expression profiling and identification of potential molecular targets for therapy in pulmonary large-cell neuroendocrine carcinoma. Exp Ther Med 2011;2:1041-5. [Crossref]

2. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Tumours of the lung. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al., editors. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. WHO Health Organization Classification of Tumours. Vol 10. Lyon, France: IARC Press; 2004.

3. Takei H, Asamura H, Maeshima A, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 2002;124:283-92. [Crossref]

4. Battafarano RJ, Fernandez FG, Ritter J, et al. Large cell neuroendocrine carcinoma: An aggressive form of non-small cell lung cancer. J Thorac Cardiovasc Surg 2005;130:166-72. [Crossref]

5. Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991;15:529-53. [Crossref]

6. Travis WD, Brambilla E, Burke AP, et al, editors. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Geneva: WHO Press; International Agency for Research on Cancer. 2015.

7. Glisson BS, Moran CA. Large-cell neuroendocrine carcinoma: controversies in diagnosis and treatment. J Natl Compr Canc Netw 2011;9:1122-9. [Crossref]

8. Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70-6. [Crossref]

9. Le Treut J, Sault MC, Lena H, et al. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. Ann Oncol 2013;24:1548-52. [Crossref]

10. Travis WD, Giroux DJ, Chansky K, et al. International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the inclusion of bronchopulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2008;3:1213-23. [Crossref]

11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47. [Crossref]

12. Fasano M, Della Corte CM, Papaccio F, et al. Pulmonary Large-Cell Neuroendocrine Carcinoma From Epidemiology to Therapy. J Thorac Oncol 2015;10:1133-41. [Crossref]

13. Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70-6. [Crossref]

14. Iyoda A, Hiroshima K, Baba M, et al. Pulmonary large cell carcinomas with neuroendocrine features are high grade neuroendocrine tumors. Ann Thorac Surg 2002;73:1049-54. [Crossref]

15. Sun JM, Ahn MJ, Ahn JS, et al. Chemotherapy for pulmonary large cell neuroendocrine carcinomas,similar to that for small cell lung cancer or non-small cell lung cancer? Lung Cancer 2012;77:365-70. [Crossref]

16. Veronesi G, Morandi U, Alloiso M, et al. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung Cancer 2006;53:111-5. [Crossref]

17. Paci M, Cavazza A, Annessi V, et al. Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. Ann Thorac Surg 2004;77:1163-7. [Crossref]

18. Iyoda A, Hiroshima K, Moriya Y, et al. Prognostic impact of large cell neuroendocrine histology in patients with pathological stage 1a pulmonary non-small cell carcinoma. J Thorac Cardiovasc Surg 2006;132:312-5. [Crossref]