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Original Article

Characteristics of Patients with Large-Cell Neuroendocrine Carcinoma of the Lung

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Abstract

OBJECTIVES: Neuroendocrine tumors of the lungs are a clearly different group of tumors with definite ultrastructural, immunohistochemical, and molecular features. We reported and analyzed the incidence, clinicopathological features, surgery rates, responses to first-line therapy, and survival outcomes of this rare condition according to our lung cancer patient database.

MATERIALS AND METHODS: We retrospectively collected the data of 62 patients who were histopathologically diagnosed with large cell neuroendocrine carcinoma of lung (LCNEC) between January 2010 and January 2016.

RESULTS: The patients were predominantly (95%) men (male:female=59:3) with their average age being 60.3±8.6 years. Diagnosis was made by the fine-needle aspiration biopsy (NAB) in 7 patients, bronchoscopic transbronchial biopsy in 13, and surgery in 42. Nearly 43.5% of the patients presented with the tumor in the right upper lobe. Additionally, tumors of 46.8% patients could be observed in peripheral locations. Sixteen patients presented with stage 1, 17 with stage 2, 15 with stage 3, and 14 with stage 4. Median progression-free survival (PFS) was 29 months (SE: 12.2) (95% CI, 5.2–52.8 months). Progression-free survival (PFS) was significantly better in patients with low N, M0, early stage, p63 positive, and TTF-1 positive across the entire cohort. Overall survival (OS) was significantly better in patients with comparatively lower N, M0, low stage, and peripheral location.

CONCLUSION: This study demonstrated a single-center experience with clinicopathologic factors and survival outcomes of LCNEC patients.

KEYWORDS: Large-cell neuroendocrine carcinoma of the lung, overall survival, progression-free survival, stage, TTF-1

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INTRODUCTION

Neuroendocrine tumors of the lungs are a 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 clinico-pathologic features, diagnosis, and treatment of our patients with large cell neuroendocrine carcinoma of the lung, to contribute to the literature.

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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, bronchoscopic 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.

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 (81)
Pneumonectomy	7 (16.7)
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)

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, CK 7 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 2. Progression-free survival

	Median (SE)	%95 CI	p
Diagnostic pattern			
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

	Median (SE)	%95 CI	p
Diagnostic pattern			
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	

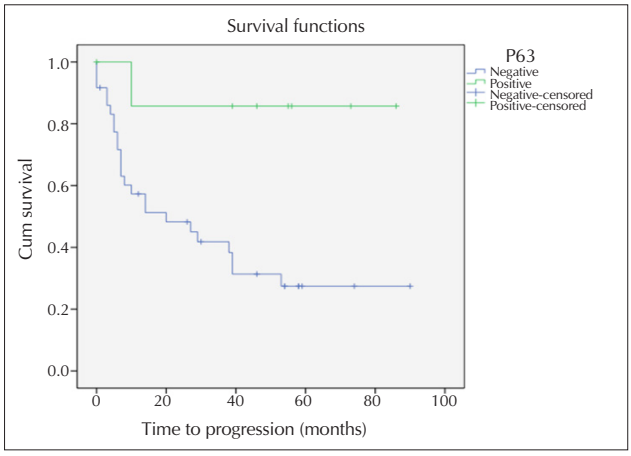

Figure 1. Correlation between cumulative survival and p63 positivity

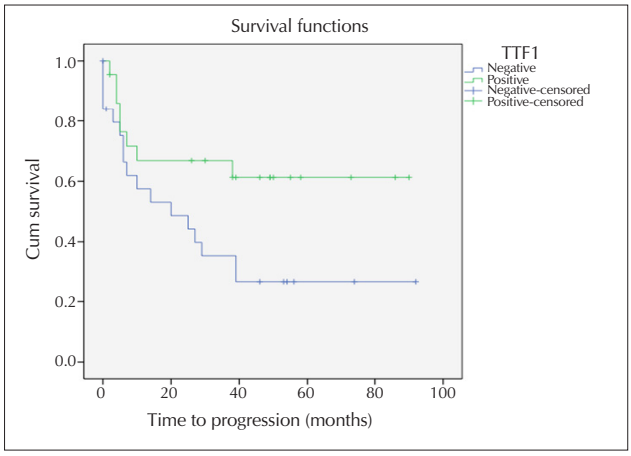

Figure 2. Correlation between cumulative survival and TTF1 positivity

cantly poorer in patients who demonstrated disease progression requiring palliative radiotherapy.

DISCUSSION

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 associated with the disease stages, clinico-pathologic features, rates of surgery, responses to first-line therapy, and survival outcomes 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 demographics in this disease. The diagnoses were mainly performed via surgery (42/62) in our cohort of patients. In the literature, most LCNECs have been postoperatively diagnosed 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 currently 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), specifically with regard to the adjuvant setting. Only one patient received neoadjuvant chemotherapy. A certain progression was observed in 32 patients, of which 16 were treated after the progression. Five patients received second-line chemotherapy. We were unfortunately unable to calculate 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.

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

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