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Large cell neuroendocrine carcinoma: retrospective analysis of 24 cases from four oncology centers in Turkey

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Abstract

Background: Large cell neuroendocrine carcinoma (LCNEC) of the lung is classified as a variant of large cell lung carcinoma by the World Health Organization, however, the clinical and biological behavior of LCNEC resembles small cell lung carcinoma (SCLC) with a high mitotic index and a positivity of tumor cells with neuroendocrine markers. As there have only been a small number of patients with LCNEC recorded in literature, there is no consensus about the management of this subset. In the present study, we evaluated the incidence and prognosis of LCNEC in four oncology centers in Turkey.
Method: We analyzed 24 patients with diagnoses of LCNEC from 3138 non-small cell lung cancer patients who were diagnosed and treated between 2008 and 2010 in four different medical oncology centers in Turkey.
Results: The median age was 56 (range; 36–64) and most patients were male, with three women included in the study. Ten out of 24 patients (41.6%) had locally advanced or metastatic disease, therefore, surgery could not be performed. Five patients (20.8%) were staged with stage I, six (25%) with stage II, five (20.8%) with stage III, and eight (33.3%) with stage IV. All patients had a history of smoking. Nine patients received chemotherapy postoperatively. At the 14.4-month follow-up period (range; 3–59) the median overall survival (OS) and progression-free survival (PFS) rates were 32.7 and 9.5 months respectively. Tumor, node, metastasis (TNM) stage, performance status (PS) and the performance of surgery were significantly related to rates of both OS and PFS ($P < 0.05$).
Conclusion: LCNEC was generally diagnosed postoperatively. Prognosis of LCNEC is poor and surgery has not proven an effective solution for long-term survival, therefore, adjuvant chemotherapy has been suggested.

Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a very rare tumor which was firstly defined by Travis *et al.* in 1991 as high grade neuroendocrine tumors which are placed between intermediate grade atypical carcinoid and high grade small-cell lung cancer (SCLC) according to biological and light microscopic characteristics.[1] Although LCNEC is a rarely seen lung cancer, the exact incidence of this tumor type is not known because LCNEC may have been diagnosed in the past as SCLC, atypical carcinoid, squamous cell carcinoma or adenocarcinoma. The World Health Organization (WHO) defined LCNEC as a variant of large cell lung carcinoma in 1999.[2] Although, LCNEC is classified as a non-small cell lung cancer (NSCLC), its clinical and biological behavior resembles small cell lung cancer (SCLC).

The preoperative diagnosis of LCNEC from biopsy specimens is difficult, therefore, the incidence of LCNEC is not known in patients who have not undergone surgery. LCNEC is generally diagnosed in the advanced stage when tumors have high rates of mitosis and lymph node metastasis.[3] Jiang *et al*. reported 22 cases of LCNEC out of 766 primary lung cancers postoperatively.[4] The morphologic features of LCNEC are similar to NSCLC with organoid, palisading rosettes, high mitotic rates (>10mitosis/10 high power fields), necrosis, large cell size with low nuclear/cytoplasm ratio, and clear nucleoli.[5,6] LCNEC also has neuroendocrine features with at least one positive neuroendocrine marker.[5] Immunohistochemical panels including chromogranin, synaptophysin, and CD56 are used to identify neuroendocrine differentiation.[7] In nearly 90% out of 87 cases of LCNEC studied by Takei *et al*. tumor cells were stained with chromogranin, synaptophysin and neuron cell adhesion molecule – 68% of them stained with all three markers and 15% stained with only one of them.[8]

Patients diagnosed with LCNEC had poor prognoses with 5-year survival rates of between 15% and 57%.[5] In a study by Iyoda *et al*. the 5-year survival rates and 5-year disease free survival rates were 35.3% and 27.4% respectively.[3] Even in stage I patients, prognosis was revealed as worse than adenocarcinoma or squamous cell carcinoma. While the 5-year survival rate of patients with stage IA LCNEC was 54.5%, this rate was 89.3% for stage IA adenocarcinoma or squamous cell carcinoma.[9] Zacharias *et al*. presented 15 patients with LCNEC and six patients with large cell carcinoma with neuroendocrine morphology, without neuroendocrine marker positivity. They documented the 5-year survival rate of the entire group, at stage I, II and III were 88%, 47% and 28% respectively.[7]

In our country, NSCLC is the most commonly seen malignancy and the leading cause of cancer death in men. LCNEC is also the most aggressive subtype of NSCLC. Because of its rarity and the difficulty in differential diagnosis, the optimal treatment strategy is not known. In cases of early diagnosis, surgery can be performed to improve chances of survival. In the current study, we analyzed survival, treatment protocol, and prognostic factors for LCNEC from four centers in Turkey.

Material and methods

We reviewed 24 patients with diagnoses of LCNEC from the medical data of 3138 NSCLC patients who were diagnosed and treated between 2008 and 2010 in four different oncology centers in Turkey. Clinical information, such as gender, performance status, operation type, tumor size, lymph node metastasis, tumor stage, and whether chemotherapy had been performed, were obtained from patients' medical records after informed consent was received from either the patients or their relatives.

For diagnosis, tissues obtained from biopsy or resection were stained with hematoxylin-eosin. Pathologists at the four different centers reviewed all specimens and diagnoses were confirmed based on World Health Organization (WHO) criteria.[2] CD56, chromogranin, synaptophysin, and neuron specific enolase, were used as immunohistochemical markers. Patients were staged according to the American Joint Committee on Cancer (AJCC), 7th version.[10]

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test. Overall survival (OS) was measured from initial diagnosis until the date of the patient's death or the patient's last contact. Progression-free survival (PFS) was defined as the time from initial diagnosis until the disease progression, date of death or the patient's last contact. Univariate analyses were carried out to evaluate important prognostic factors, then multivariate analysis with the Cox proportional hazards model was performed to further analyze independent prognostic factors, which were found in the univariate analysis predicting OS and PFS. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All P-values were two-sided in the tests and *P*-values equal and less than 0.05 were considered to be statistically significant.

Results

At the time of diagnosis, the median age of the patients was 56.5 years (range; 36–64). Three of the patients were female. All patients had a history of cigarette smoking. The Eastern Cooperative Oncology Group (ECOG) PS were 0 and 1 for 60.9% of patients, 2 in 34.8% of patients and 3 in one patient (4.3%).

Diagnoses of LCNEC were confirmed with surgery in 14 patients, with lobectomy for 10 patients, pneumonectomy for one, and wedge resection for three patients. However, LCNEC was diagnosed by bronchoscopic biopsy in 10 patients. There was no postoperative mortality in patients who underwent surgery. Lymph node metastasis was detected in 10 patients (41.6%) during surgery. The characteristics of the patients are shown in Table 1.

All tissue specimens had neuroendocrine characteristics, such as organoid trabecular, rosette or palisading growth. Tumor cells had large cell with low nuclear-cytoplasmic ratios and clear nucleoli. The mitotic rate was greater than 10/10 high power field. Immunohistochemically, 85.7% of tumor cells were stained positive with synaptophysin, 63.6% positive with chromogranin, 57.1% positive with neuron specific enolase (nse), and 75% positive with CD56. None of the tumor cells were stained positive with only nse.

Five patients were staged as stage I, six as stage II, five as stage III and eight as stage IV. Eight patients who had

Table 1 The characteristic of patients, treatment type and survival

Patients	Gender	Age	Operation	Stage	Chemotherapy	OS (mo)	PFS (mo)
1	Male	60	RLL	IA	Absent	3	3
2	Male	58	RP	IIB	Cisp-etop	39.1	30
3	Male	53	Absent	IV	Cisp-etop	11.5	9.5
4	Male	60	RUL	IIA	Carbo-etop	35.8	35.8
5	Male	48	LUL	IA	Cisp-etop	15.6	15.6
6	Male	64	RUL	IIB	Absent	2.2	2.2
7	Female	49	LUL	IV	Cisp-etop	5.6	5.6
8	Male	53	LUL	IIA	Cisp-etop	4.1	4.1
9	Male	56	Absent	IV	Cisp-etop	4	4
10	Female	57	LLL	IIIA	Cisp-etop	9.7	9.7
11	Male	50	Wedge	IIIB	Cisp-etop	8.2	8.2
12	Male	58	Wedge	IV	Cisp-etop	13.2	7.6
13	Female	58	Wedge	IA	Absent	28.6	28.6
14	Male	53	LLL	IB	Absent	58.7	58.7
15	Male	58	LUL	IB	Cisp-etop	32.7	12.4
16	Male	54	Absent	IV	Cisp-etop	23	9.2
17	Male	56	Absent	IV	Cisp-etop	3.1	3.1
18	Male	64	Absent	IIIB	Cisp-etop	16.3	11.6
19	Male	56	Absent	IV	Cisp-etop	6.7	6
20	Male	36	Absent	IV	Cisp-etop	6.5	4.1
21	Male	63	Absent	IIIB	Carbo-etop	2.2	2.2
22	Male	62	Absent	IV	Cisp-etop	8.6	6.3
23	Male	48	LUL	IIB	Cisp-etop	4.9	4.9
24	Male	58	Absent	IIIB	Carbo-etop	2.5	2.5

carbo-etop, carboplatin-etoposide; cisp-etop, cisplatin-etoposide; LLL, left lower lobectomy; LUL, left upper lobectomy; mo, month; OS, overall survival; PFS, progression free survival; RLL, right lower lobectomy; RP, right pneumonectomy; RUL, right upper lobectomy.

undergone surgery received chemotherapy postoperatively. However, six patients who had surgery did not received chemotherapy postoperatively – two of these six were staged as IA, two as IB, one as IIB and one as IIA. Chemotherapy was recommended for a patient with stage IIB disease, but the patient refused it. Approximately 42% of the patients (n = 10) were diagnosed via biopsy, without surgery, because of stage IIIB (three patients) or stage IV (seven patients). The majority of patients received a combination chemotherapy regimen including cisplatin and etoposide, and only three patients were treated with carboplatin instead of cisplatin in combination with cisplatin because of the presence of comorbidities. During chemotherapy, although grade 4 toxicity was not seen, grade 3 neutropenia was seen in two patients with one hospitalization due to febrile neutropenia, and one patient hospitalized due to deep venous thrombosis.

During the 14.4 months (range: 3–58) of follow-up, median OS and PFS rates were 32.7 and 9.5 months respectively (Figs 1, 2). Recurrence or progression was detected in 13 (54.2%) of the 24 patients. Fifty percent of these patients experienced progression because of cranial metastasis. Tumor, node, metastasis (TNM) stage, the performance of surgery and PS status were related to both OS and PFS ($P < 0.05$). The one-year OS rate of patients who underwent surgery was better (88.9%) than those who did not undergo surgery (51.9%) ($P = 0.04$). The median OS time was 23 months for patients who did not undergo surgery, however, median OS couldn't be reached in patients who had not undergone surgery. Median PFS times were 30.8 and 6.3 months for patients whether they had undergone surgery or not ($P < 0.001$). The median PFS was better in patients with

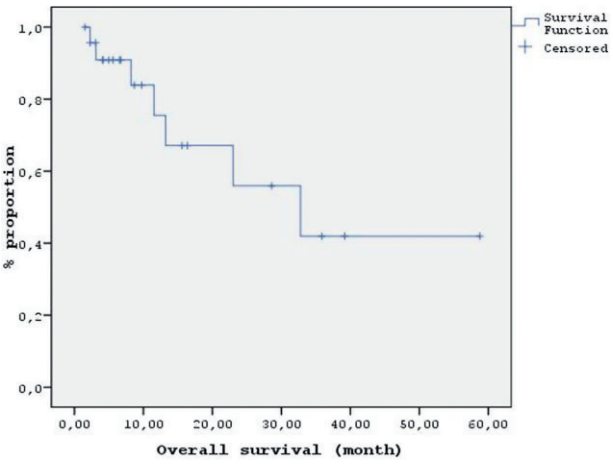

Figure 1 Overall-survival curve of patients with large cell neuroendocrine carcinoma (LCNEC).

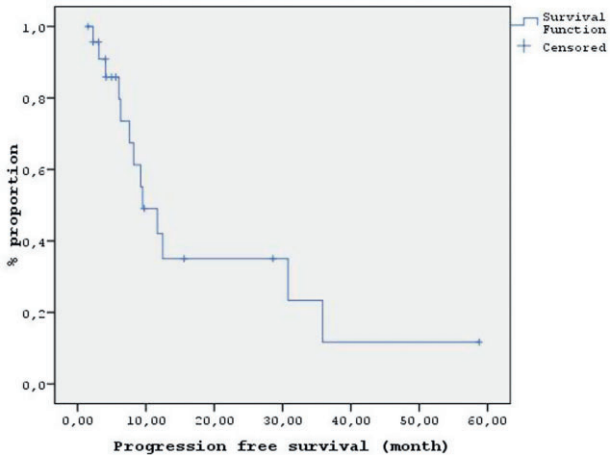

Figure 2 Progression free survival curve of patients with large cell neuroendocrine carcinoma (LCNEC).

early stage disease (it couldn't be reached in stage I and 30.8 month for stage II) compared with advanced stage (8.2 month for stage III, 6.3 month for stage IV) ($P < 0.001$). The median OS was also better in patients with early stage disease than advanced stage ($P = 0.02$). Patients with a low PS score (0 or 1) had significantly better OS and PFS rates than patients with a PS of 2 or 3 ($P < 0.001$)(Table 2). We couldn't find any independent prognostic factors predicting OS or PFS by multivariate analysis.

Discussion

In our country, NSCLC is the leading cause of cancer death among men. LCNEC is an aggressive subtype of NSCLC exhibiting biological behavior resembling SCLC and a offering poor prognosis.[5] Due to difficulty in the differential diagnosis of LCNEC, we do not know the real incidence in our

Table 2 The results of univariate analysis

Patient characteristics	No (%)	2 year PFS rate (%)	P	2 year OS rate (%)	P
Gender			0.1		0.3
Female	3 (12.6)	na		na	
Male	21 (87.4)	27.8		50	
Ps			<0.001		<0.001
0	4 (16.6)	na		na	
1	11 (45.8)	62		71.1	
2	8 (33.3)	0		0	
3	1 (4.3)	0		0	
Operation			<0.001		<0.001
Present	14 (58.3)	64.8		76.2	
Absent	10 (41.7)	0		0	
Tumor size			0.03		0.9
≤ 4 cm	7 (35)	68.9		85.7	
> 4 cm	13 (65)	16.5		45	
T stage			0.2		0.5
T1a	3 (12.5)	na		na	
T1b	1 (4.5)				
T2a	5 (20.8)				
T2b	3 (12.5)				
T3	7 (29.2)				
T4	5 (20.8)				
Lymph node metastasis			0.09		0.2
Present	10 (41.6)	14.6		36.5	
Absent	14 (58.4)	57.1		73.3	
Stage			0.001		0.02
I	5 (29.4)	75		na	
II	6 (23.5)	50		na	
III	5 (11.8)	0		50	
IV	8 (35.3)	0		29	
Adjuvant CT			0.2		0.8
Present	8 (71.4)	26.4		64.6	
Absent	6 (28.6)	51.4		51.4	
Recurrence					0.05
Present	13 (54.2)			40.3	
Absent	11 (45.8)			na	

CT, chemotherapy; no, number; OS, overall survival; PFS, progression free survival.

country and, therefore, we reviewed the survival, treatment protocol, and prognostic factors for LCNEC from four different oncology centers in Turkey. According to WHO criteria, at least one neuroendocrine marker is required for the diagnosis of LCNEC; approximately 70% of tumors in our study were stained positive with both synaptophysin and chromogranin.[11] In our study 85.7% of tumor cells were positive with synaptophysin, 63.6% positive with chromogranin, 57.1% with nse and 75% with CD56, immunohistochemically. None of the tumors were positive with only nse.

Jungraithmayr *et al.* reported the incidence of LCNEC as 0.6% (eight patients) from 2053 resected lung cancers.[12] Although we evaluated 3138 NSCLC, we found only 24 patients with a diagnosis of LCNEC. Diagnosis of LCNEC is problematic because of small biopsy specimens and diagnostic difficulties. Unfortunately, nearly half of our patients (41.7%) were diagnosed by biopsy in advanced stage. The incidence of LCNEC in our study was 0.7% – this result may be related to the low incidence of early stage diagnosis and low surgery rate for NSCLC. Moreover, immunohistochemical study of all biopsy specimens may not have been performed adequately. Many patients with LCNEC diagnosed by biopsy may have been incorrectly diagnosed and treated as SCLC or NSCLC.

Veronesi *et al.* reviewed 144 patients with LCNEC in a multicenter study.[13] All of their patients underwent surgery; the median age was 63 years with male predominance. All of our patients were smokers and 87.5% were male, similar to factors reported in literature.[5,6,13,14] Most of their patients were diagnosed as early stage disease (50% stage I, 20% stage II) with a 5-year survival rate of 42.5%. Out of years from 12 different study ranges and at five years, Veronesi *et al.* observed OS rates between 0% and 57% for all stages of patients. These studies included between nine and 144 patients. In their study, stage III disease, age, and surgery type were independent prognostic factors for OS by multivariate analysis. We reviewed only 24 patients in four different centers in our country. Unlike results found in literature, in our study, surgery could only be performed for 14 patients, with the diagnosis of the remaining 10 patients confirmed by biopsy. We could not find any independent prognostic factors for OS or PFS by multivariate analysis.

Hage *et al.* evaluted seven patients with LCNEC who had undergone surgery. Three of them received adjuvant chemotherapy and had a seven to 39 month range of median OS.[14] Jiang *et al.* reported a 2.8% (22 cases) frequency of LCNEC in their 766 resected NSCLC series.[4] In their study they found that one and 5-year survival rates were 58.8% and 44.8%. Battafarano *et al.* reported incidence and 5-year survival of LCNEC at 2.2% (45 cases) and 30% respectively for their 2099 patients who underwent surgery.[15] In their study, the 5-year survival of patients with LCNEC was significantly poorer than for patients with large cell lung carcinoma. The tumors that had neuroendocrine morphological characteristics and neuroendocrine differentiation were diagnosed as LCNEC, rather than NSCLC. The study undertaken by Battafarano *et al.* included patients with tumors exhibiting both LCNEC and adenocarcinoma characteristics. All of our patients were pure LCNEC morphologically and demonstrated at least one positive neuroendocrine marker.

Because of the rarity of diagnosis of LCNEC, there are only a small retrospective number of series available for study. Therefore, an optimum therapy has not yet been defined. In the literature, most studies reported resected LCNEC; the effect of chemotherapy or radiotherapy on survival or prognosis has not yet been well established. The survival of patients with LCNEC after surgery has been poor, therefore, there is no consensus whether these tumors should be considered and treated as SCLC or NSCLC. Iyoda *et al.* showed that adjuvant chemotherapy with cisplatin and etoposide was effective in LCNEC patients.[16] Paci *et al.* evaluated 48 resected LCNEC patients and reported that survival of these patients was not different from the survival of SCLC patients who were treated at the same time.[17] Dresler *et al.* indicated that patients who received adjuvant chemotherapy for stage I LCNEC had a poorer prognosis than those who did not receive chemotherapy.[18] In contrast, Iyoda *et al.* confirmed a survival benefit of chemotherapy for stage I disease.[19] The effectiveness of adjuvant chemotherapy for stage IA LCNEC is controversial.[5] In our study, one of our three stage IA LCNEC patients was treated with adjuvant chemotherapy All of our patients who underwent surgery received platin and etoposide (as they would have if they had been treated for SCLC), postoperatively, but we couldn't determine any relation between the presence of chemotherapy and survival. This may be related to the small number of patients in our study. Although Veronesi *et al.* couldn't find a statistically significant relationship between survival and chemotherapy for stage I disease either, in their study, 3-year survival was better for patients who received chemotherapy than those who did not (100% vs. 58%, $P = 0.07$).[13] Three of our patients with stage II disease, two with stage III, and one patient with stage I, were treated with chemotherapy postoperatively. We found only surgery type and stage were related to both OS and PFS. This is commonly the case, as patients who could undergo surgery were early stage, so their prognosis was better than advanced stage.

Iyoda *et al.* reported 36 recurrences of 72 LCNEC patients during three years of follow-up.[20] Patients who received adjuvant chemotherapy had lower recurrences than those who had not received adjuvant chemotherapy. They reported that the 5-year DFS for their whole group was 42.7%. In addition, they found that the 5-year OS rate for patients with recurrent tumors was worse than the rate for patients without recurrence (12.5% vs. 88.7%). Recurrences were normally found in the lymph nodes (25%), lung (17%) and brain (15%). In 36

recurrent patients, the ratios of metastatic sites were 50% for lymph nodes, 33% for lung, and 31% for brain. In our study 54.2% of recurrences were detected during the median 14.4 months (range; 3–58) of follow-up. The most frequent recurrence site in our study was the brain at 50%, which is similar to what has been reported in the literature.

Conclusion

Because of the poor prognosis of LCNEC, this histological class of NSCLC should be carefully distinguished. It would be helpful if all surgical specimens used to diagnose SCLC, NSCLC, and lung neuroendocrine carcinoma were re-evaluated retrospectively to reveal the real incidence rate of LCNEC in our country.

Disclosure

No authors report any conflict of interest.

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