

## Clinical Features of Large Cell Neuroendocrine Carcinoma: A Population Based Overview

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**Background:** Pulmonary large cell neuroendocrine carcinoma (LCNEC) is an orphan disease and few data are available on clinical characteristics. Therefore, we analyzed LCNEC registered in the Netherlands Cancer Registry (NCR) and compared data with small cell lung cancer (SCLC), squamous cell (SqCC) and adenocarcinoma (AdC).

**Patients and Methods:** Histologically confirmed LCNEC ( $N=952$ ), SCLC (11,844), SqCC (19,633) and AdC (24,253) cases were selected from the NCR (2003-2012). Patient characteristics, metastases at diagnosis ( $\geq 2006$ ) and overall survival (OS) were compared for stage I-II, III and IV disease. Multivariate COX regression analysis was performed including age, sex, TNM edition and T/N-stage for stage I-II, III and IV disease. Additionally, stage I/II surgically treated patients including the co-variate adjuvant chemotherapy (yes/no), and stage IV chemotherapy treated patients were analyzed separately. Non-proportionality was observed in stage I-II disease and therefore time-dependent Hazard ratios were reported.

**Results:** LCNEC increased from 56 patients in 2003 to 143 patients in 2012, attributing 0.9% of all lung cancers in this time period. Stage IV LCNEC patients ( $N=383$ ) commonly had metastasis in liver (47%), bone (32%) and brain (23%), resembling SCLC. Median OS (95% confidence interval) of stage I-II, III and IV LCNEC was 32.4 (22.0-42.9), 12.6 (10.3-15.0) and 4.0 (3.5-4.6) months, respectively. In stage I-II surgically treated and stage IV chemotherapy treated LCNEC patients, the multivariate adjusted OS resembled SCLC and was poorer than that of SqCC and AdC (Table 1). However, frequency of treatment with adjuvant chemotherapy in surgically resected stage I-II LCNEC (23%) resembled SqCC (15%) and AdC (14%) more than SCLC (75%).

**Conclusion(s):** Diagnosis of LCNEC increased over the past 10 years. Metastatic pattern of LCNEC resembles SCLC as does OS in multivariate analysis. However, early stage treatment strategies seem more comparable to SqCC and AdC.

**Table 1. Multivariate analysis of overall survival for LCNEC compared to SCLC, SqCC and AdC.**

Stage comparison	variable	Histology						
		LCNEC	SCLC	SqCC		AdC		
		HR	HR	95% CI	HR	95% CI	HR	95% CI
<b>Stage I-II</b>	Adjusted (1)	1	1.85	1.27-2.69	1.15	0.82-1.63	0.84	0.59-1.19
	< 10 months*	1	1.56	1.21-2.00	0.65	0.52-0.80	0.64	0.52-0.80
<b>Stage I-II surgical cohort</b>	Adjusted (2)	1	0.71	0.33-1.50	0.72	0.49-1.05	0.56	0.38-0.82
	≥ 10 months*	1	1.14	0.77-1.69	0.47	0.37-0.60	0.52	0.41-0.66
<b>Stage III†</b>	Adjusted (1)	1	0.93	0.78-1.10	0.88	0.74-1.04	0.86	0.73-1.02
	< 10 months*	1	0.87	0.79-0.95	0.79	0.72-0.87	0.79	0.72-0.86
<b>Stage IV chemotherapy cohort</b>	Adjusted (3)	1	1.06	0.91-1.23	0.85	0.73-0.99	0.85	0.73-0.99
	< 10 months*	1	1.06	0.91-1.23	0.85	0.73-0.99	0.85	0.73-0.99

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma; SqCC, squamous cell carcinoma; AdC, adenocarcinoma; HR, Hazard-ratio; CI, confidence interval; TNM, Tumor-Node-Metastasis classification.

1 age, sex, TNM edition, T stage, N stage

2 age, sex, TNM edition, T stage, N stage, adjuvant chemotherapy

3 age, sex, TNM edition, T stage, N stage

\*Time stratification used to counter non-proportionality (occurring for stage I-II).

† Insufficient patients with LCNEC therapeutically treated (e.g. with chemo-radiotherapy or chemotherapy) to allow for controlling of treatment.

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