

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

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## Background

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a neuroendocrine malignancy with >10 mitosis 2mm<sup>2</sup> and abundant cytoplasm/clear nuclei.

**Incidence** of LCNEC is low (1.5-3%) and majority of data are retrieved from surgically resected series. Few studies have analyzed the **metastatic pattern**. Moreover, optimal **disease management** (i.e. treat as small cell lung cancer (SCLC) or non-small cell lung cancer) is debated.

## Study aim

Here we report and compare clinical characteristics, treatment, metastatic pattern and overall survival (OS) of LCNEC with SCLC, Squamous cell carcinoma (SqCC) and Adenocarcinoma (AdC) in the Netherlands from 2003-2012.

## Patients and methods

Retrospective analysis, data retrieved from the Netherlands Cancer Registry (NCR) cases included from 01-2003 until 12-2012

### Registered data:

- Age, gender, TNM classification (TNM-6 <2010, TNM-7 ≥2010), year of diagnosis, first line therapy and metastases at diagnosis (>2005)

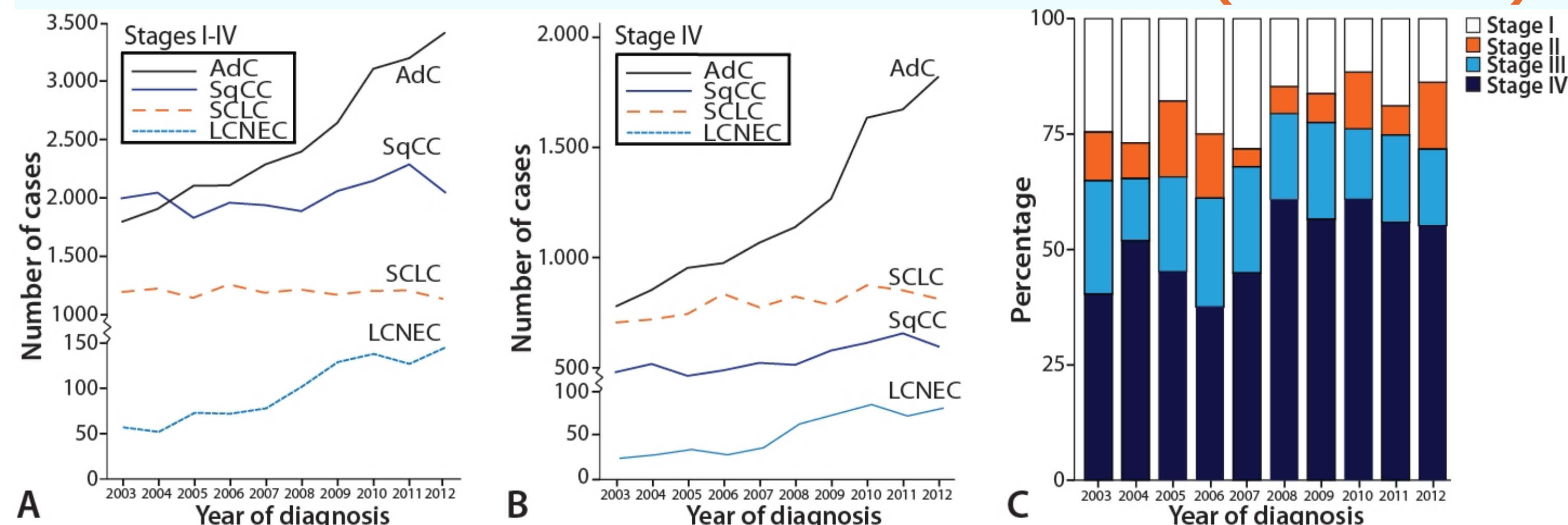
### Exclusion:

- Diagnosis on cytology specimen
- Incomplete vital status follow-up or TNM
- Metastatic pattern analysis only:**
  - Diagnosed ≤ 2005 or metastasis not documented in NCR
  - Previous malignancy ≤5 years
  - Solitary pulmonary metastasis in TNM-6

### Analysis:

- Multivariable Cox regression models stratified for stage and treatment (stage I-II + surgery, stage IV + chemotherapy)
- Time stratification was used to counter non-proportionality in stage I-II analysis

## Incidence of LCNEC has increased with 2.5 fold (2003-2012)



## Results: clinical characteristics and treatment of LCNEC

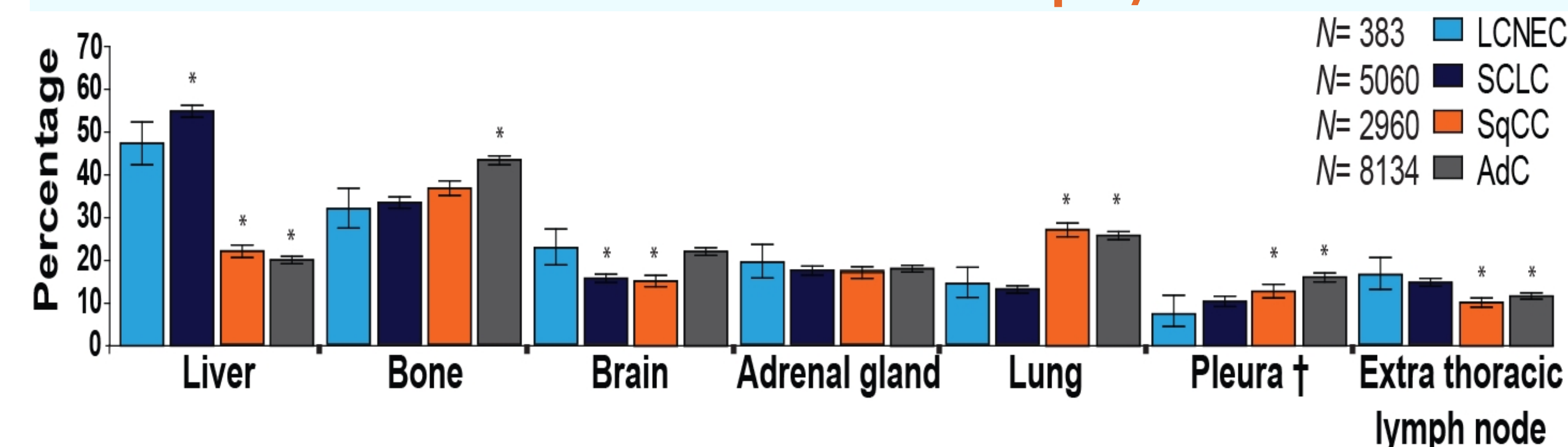
58,074/59,283 patients were selected from the NCR. From the 25,990 cases with stage IV disease selected, 16,537 were evaluable for metastatic pattern analysis.

- LCNEC **stage description reflects AdC** most closely and patients with LCNEC were frequently surgically treated in stage I-II disease
- Patients with LCNEC received **less (adjuvant) chemotherapy** than SCLC

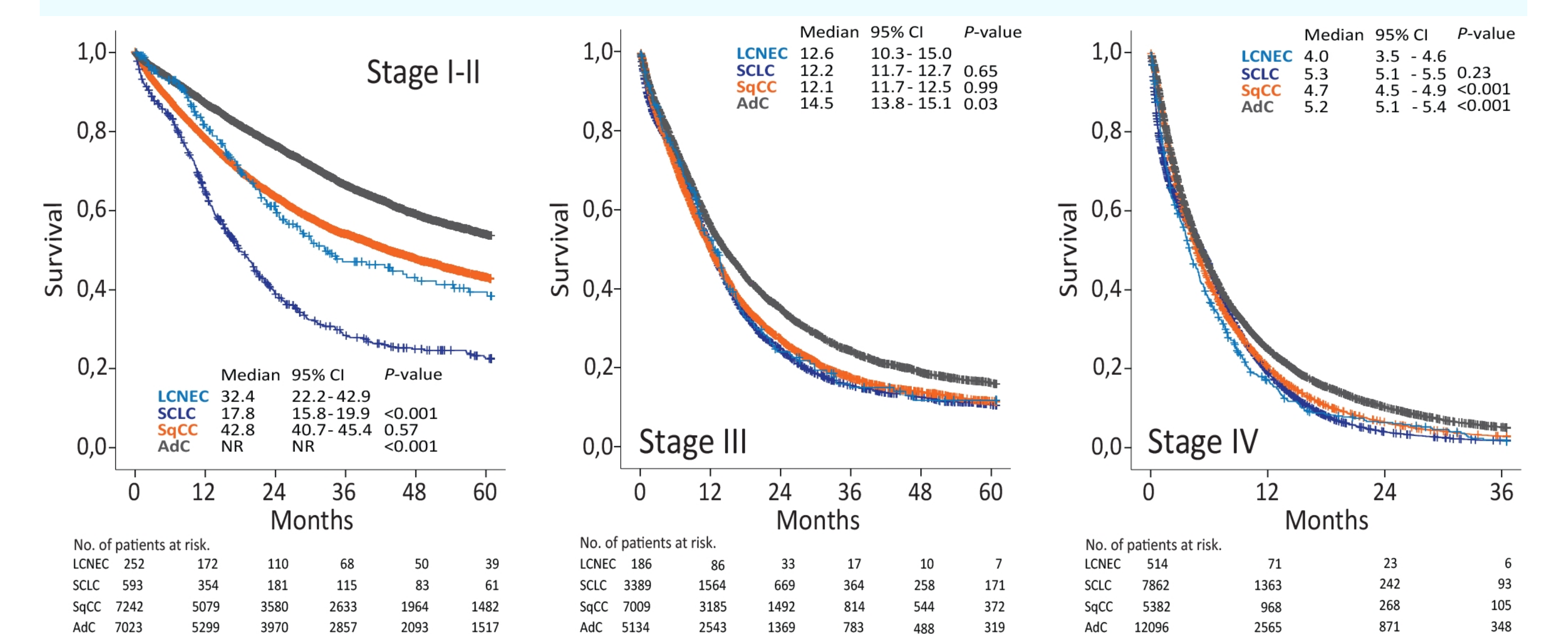
Variable	Histology						P-values versus LCNEC	
	LCNEC (N=952)		SCLC (N=11,844)		SqCC (N=19,633)			AdC (N=24,253)
<b>Age</b>	No.	%	No.	%	No.	%	No.	%
Mean(SD)	65.5 (10.5)		66.7 (9.7)		68.8 (9.4)		64.6 (10.7)	
Median	66		67		70		65	
IQR	52-80		53-81		57-83		49-81	
<b>Gender</b>								
Male	595	62.5	6903	58.3	15055	76.7	13404	55.3
Female	357	37.5	4941	41.7	4578	23.3	10849	44.7
<b>TNM Stage</b>								
I	162	17.0	370	3.1	4745	24.2	5318	21.9
II	90	9.5	223	1.9	2497	12.7	1705	7.0
III	186	19.5	3389	28.6	7009	35.7	5134	21.2
IV	514	54.0	7862	66.4	5382	27.4	12096	49.9
<b>Treatment in stage I-II</b>								
No treatment	4	1.6	68	11.5	564	7.8	254	3.6
Resection	220	87.3	114	19.2	5039	69.9	5816	82.8
RT	17	6.7	26	4.4	1008	13.9	601	8.6
CT & RT	4	1.6	270	45.5	288	4.0	109	1.6
CT	2	0.8	94	15.9	111	1.5	55	0.8
Other	5	2.0	21	3.5	232	3.2	188	2.7
<b>Stage I-II resections</b>								
Adjuvant CT	51	23.2	91	75.4	769	15.3	786	13.5
<b>Treatment in stage III</b>								
No treatment	36	19.4	473	14.0	1346	19.2	801	15.6
Resection	39	21.0	32	0.9	1066	15.2	1254	24.4
RT	20	10.8	55	1.6	1120	16.0	362	7.1
CT & RT	57	30.6	1794	52.9	2252	32.1	1492	29.1
CT	27	14.5	912	26.9	888	12.7	879	17.1
Other	7	3.8	123	3.6	337	4.8	346	6.7
<b>Stage III resections (neo) adjuvant CT</b>	21	53.8	26	81.3	508	47.7	707	56.4
<b>Treatment in stage IV</b>								
No treatment	235	45.7	2147	27.3	2422	45.0	4823	39.9
Resection	17	3.3	7	0.1	131	2.4	363	3.0
RT	30	5.8	49	0.6	523	9.7	435	3.6
CT & RT	22	4.3	447	5.7	325	6.0	436	3.6
CT	196	38.1	4941	62.8	1744	32.4	4735	39.1
Other*	14	2.7	271	3.4	237	4.4	1304	10.8

**Legend:** \* tested with Mann Whitney U Test; † including treatment with kinase inhibitors. Abbreviations: RT, radiotherapy; CT, chemotherapy; SD, standard deviation; IQR, inter quartile range.

## Pattern of metastasis at initial diagnosis in LCNEC resembles SCLC more than SqCC/AdC



## Overall survival of LCNEC resembles SCLC (III/IV) and is worse than that of SqCC and AdC in stage I-II and IV disease



## Prognosis of LCNEC resembles SCLC when stratified for treatment in multivariate regression analysis

**Table 2. Multivariate analysis of overall survival for LCNEC compared to SCLC, SqCC and AdC.**

Stage comparison	variable	Histology						
		LCNEC	SCLC	SqCC	AdC			
Stage I-II	Adjusted (1)							
	< 10 months*	1	1.85	1.27-2.69	1.15	0.82-1.63	0.84	0.59-1.19
surgical cohort	Adjusted (2)							
	< 10 months*	1	0.71	0.33-1.50	0.72	0.49-1.05	0.56	0.38-0.82
Stage III†	Adjusted (1)	1	0.93	0.78-1.10	0.88	0.74-1.04	0.86	0.73-1.02
	Adjusted (1)	1	0.87	0.79-0.95	0.79	0.72-0.87	0.79	0.72-0.86
Stage IV	Adjusted (1)	1	1.06	0.91-1.23	0.85	0.73-0.99	0.85	0.73-0.99

### Legend:

- Age, Sex, TNM edition, T stage, N stage
  - Age, Sex, TNM edition, T stage, N stage, Adjuvant Chemotherapy
- \* Time stratification used to counter non-proportionality (stage I-II)  
† Insufficient patients with LCNEC therapeutically treated to allow for controlling treatment.

## Conclusions

- Diagnosis of LCNEC increased 2.5 fold in 10 years time, especially stage IV disease.
- Prognosis and metastatic pattern of LCNEC resemble SCLC. However, frequency of early stage diagnosis and disease management of LCNEC seem more comparable to SqCC and AdC.
- Trials are needed to investigate optimal treatment of early stage and advanced stage LCNEC.

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