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

Jules L. Derks1, Lizza E. Hendriks1, Wieneke A. Buikhuisen2, Harry J.M. Groen3, Erik Thunnissen4, Robert Jan van Suylen5, Ruud Houben6, Ronald A. Damhuis7, Ernst-Jan M. Speel8, Anne-Marie C. Dingemans1

1: Dept. of Pulmonary Diseases, GROW - School for Oncology and Developmental Biology, Maastricht UMC; 2: Dept. of Thorax Oncology Netherlands Cancer Institute, Amsterdam; 3: Dept. of Pulmonary Diseases, UMC Groningen; 4: Dept. of Pathology, VU UMC, Amsterdam; 5: Dept. of Pathology, Jeroen Bosch Hospital, e Hertogenbosch; 6: Dept. of Radiation Oncology (MAASTRO Clinic), GROW - School for Oncology and Developmental Biology, Maastricht UMC; 7: Dept. of Registry and Research, Comprehensive Cancer Centre, Rotterdam; 8: Dept. of Pathology, GROW - School for Oncology & Developmental Biology, Maastricht UMC, the Netherlands

Background
Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a neuroendocrine malignancy with >10 mitosis 2mm2 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
8,074/59,283 patients were selected from the NCR. From the 25,990 cases with stage IV disease selected, 16,537 were evaluated 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

SCLC

TABLE 1. Baseline characteristics according to morphological subtype

Legend:
- 1) Dept. of Pulmonary Diseases, GROW - School for Oncology and Developmental Biology, Maastricht UMC; 2) Dept. of Thorax Oncology Netherlands Cancer Institute, Amsterdam; 3) Dept. of Pulmonary Diseases, UMCG, Groningen; 4) Dept. of Pathology, VU UMC, Amsterdam; 5) Dept. of Pathology, Jeroen Bosch Hospital, e Hertogenbosch; 6) Dept. of Radiation Oncology (MAASTRO Clinic), GROW - School for Oncology and Developmental Biology, Maastricht UMC; 7) Dept. of Registry and Research, Comprehensive Cancer Centre, Rotterdam; 8) Dept. of Pathology, GROW - School for Oncology & Developmental Biology, Maastricht UMC, the Netherlands

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.

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