A Single-Institution Analysis of the Surgical Management of Pulmonary Large Cell Neuroendocrine Carcinomas

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Background. **Large cell neuroendocrine carcinoma (LCNEC) is an uncommon tumor of the lung and represents approximately 3% of all lung cancers. LCNEC displays biological behaviors resembling those of small cell lung carcinomas and features of high-grade neuroendocrine tumors. LCNEC of the lung are considered aggressive. Reported prognoses are heterogeneous, and the optimum treatment remains undefined.**

Methods. **We conducted a retrospective study of all patients who were treated for LCNEC in our Department of Thoracic Surgery between May 2005 and December 2013. Primary outcomes of interest were patient survival and prognostic factors. Kaplan-Meier analysis was performed to determine the significant predictors of overall survival.**

Results. **Within the prescribed period, 127 patients were treated for LCNEC, and 125 underwent surgical resection with curative intent. Induction chemotherapy or radiochemotherapy was given to 9 patients, and 63 patients received postoperative chemotherapy. Complete resection was achieved in 99.2%. The overall 1-, 3- and 5-year survival rates were 83.7%, 63.2%, and 53.8% of all patients, and the 5-year survival in patients at stages I, II, and III was 64.5%, 40%, and 29.7%. There was a significant survival difference at 5 years between pT1/2 (58.5%) and pT3 tumors (22.4%; $p = 0.043$) and for patients with lymphatic involvement (L0 vs L1, $p = 0.001$; pN1 or pN2 vs pN0, $p = 0.04$).**

Conclusions. **Surgical treatment can achieve satisfactory results in early tumor stages, which are comparable with other non-small cell lung cancers, with a low perioperative mortality rate.**

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Pulmonary neuroendocrine tumors (NETs) represent approximately 20% of all lung cancers and can be divided into four different groups: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC). LCNEC of the lung represents a rare entity of the pulmonary NET spectrum and was first described by Travis and colleagues [1] in 1991. LCNEC was first included into the World Health Organization (WHO) classification of lung cancer 2004. LCNEC is classified as a variant of large cell carcinomas, although the tumors show clinical and biologic characteristics that are similar to those of SCLC.

A small percentage of LCNEC shows histologic heterogeneity. LCNEC may harbor components of small cell and large cell types, with adenocarcinoma, squamous cell carcinoma, and other tumor types. These cases are classified as combined LCNEC. Clinical outcomes of patients with LCNEC are reported to be similar to SCLC, with 5-year survival rates reported from 15% to 57% [2–5]. The incidence of NETs is approximately 1.35/100,000 per year and has grown in recent decades. This is mainly the result of recent lung cancer screening programs and the improvement of available diagnostic tools [6, 7].

Owing to the rarity of presentation and persistent difficulty of differential diagnosis, the prognosis and best treatment for this group of malignancies remain uncertain. LCNECs are currently mainly treated as other non-small cell carcinomas, but due to the low prevalence of LCNEC, little knowledge exists about the biology of the tumor, treatment strategies, and prognosis. Therefore, the therapeutic management of LCNEC is still controversial. To increase our knowledge of LCNEC treatment results, we retrospectively evaluated our experience with the surgical management of LCNEC patients with a special focus on prognosis and recurrence.

Patients and Methods

Our study protocol was approved by the University Duisburg-Essen Medical Faculty Ethics Committee

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(13-5363-BO), and informed consent was retrieved from all patients who were alive. Patients were identified from a prospective clinical database and from the pathology database. All patients were treated for LCNEC at the Department of Thoracic Surgery, Ruhrlandklinik Essen (Germany) from May 2005 to December 2013 and were retrospectively analyzed. Data were obtained from the medical records, pathology reports, and the cancer center database. Referring specialists were asked for missing values, and in some cases, patients or their relatives were contacted for further information.

Staging

Standard oncologic staging included computed tomography of the chest, abdomen, magnetic resonance imaging of the head, and bone scintigraphy. In the last 3 years of the study interval, positron emission tomography (PET) was integrated into the standardized staging procedure. Suspicious mediastinal nodes were further investigated with endobronchial ultrasound and transbronchial needle aspiration or mediastinoscopy, as appropriate. The clinical stage was determined for each patient by incorporating all preoperative imaging and invasive staging procedures, according to the staging guidelines.

Patients were surgically treated with the goal of complete resection. Frozen section analysis was used to confirm free margins when necessary. Anatomic resection was combined with systematic lymph node sampling or systematic dissection at the discretion of the surgeon. Patients with a N3 disease or distant metastases were precluded from curative resection. If mediastinal N2 disease was confirmed by mediastinoscopy or endobronchial ultrasound–transbronchial needle aspiration, neoadjuvant chemotherapy was prescribed and resection performed in case of a response or stable disease. Adjuvant chemotherapy was prescribed in patients with stage II and III disease and adjuvant radiotherapy in patients with postoperatively confirmed N2 disease.

Neuroendocrine morphology and positive staining for CD56, chromogranin A (CGA) or synaptophysin A (SYN-A) were mandatory criteria for histologic confirmation of LCNEC according to the World Health Organization [8]. CD56 expression was observed in 120 of the 127 patients, CGA in 105, and SYN-A in 94.

This study was conducted to evaluate patient characteristics, pathologic results, survival, and the prognostic factors of this rare disease in our hospital.

Statistical Analysis

Overall survival was defined as the interval between the date of operation and the date of death or the last follow-up visit for the patients. All patients alive at the latest follow-up were censored. Kaplan-Meier analysis was used to compute univariate comparisons between different subsets, including overall survival, T status, N status, and local lymphatic spread. The log-rank test was used to compare the survival distributions of two samples. Differences with a p value of less than 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 22.0 software (IBM Corp, Armonk, NY).

Results

Patient Characteristics and Treatment

Between May 2005 and December 2013, more than 3,000 patients were operated for non-small cell lung cancer (NSCLC) in the Department of Thoracic Surgery. Within this period, 127 patients, including 45 women (35.4%) and 82 men (64.6%), with a median age of 63.8 $\pm$ 9.9 years (range, 38 to 85 years), were treated for LCNEC.

In our LCNEC cohort, 121 patients (97.6%) were active smokers or former smokers with a history of more than 20 pack-years. Thirty of the patients (25.2%) affected by LCNEC had a history of malignancy, with lung cancer in 12 (40%) and gastrointestinal tract cancer in 7 (23%); these were the most frequent. Comorbid disease was present in 92.1% of patients, with chronic obstructive pulmonary disease in 38 (29.2%) being the commonest. Cancer-related symptoms were found in 33 patients: 25 (75.8%) reported persisting cough, 5 reported occasional hemoptysis, and 3 reported weight loss of more than 10% of their body weight within the last 3 months. No patient had a paraneoplastic syndrome.

Most tumors were detected by routine chest imaging, and the patients reported nonspecific clinical symptoms. Only 6 of 125 patients (4.8%) had an accurate preoperative diagnosis of LCNEC secured by bronchoscopy or percutaneous fine-needle punch biopsy. The tumor location was peripheral in 108 (85%) and central in 19 (15%). The upper lobes were the location of 63.1% of the tumors, with the right upper lobe in 46 (36.3%), in the left upper lobe in 34 (26.8%), followed by the right lower lobe in 22 (17.3%) and the left lower lobe in 17 (13.4%). Tumors of the middle lobe (3.1%) or central tumors affecting more than 1 lobe (3.1%) were rarely seen.

Operative Results

Primary resection was performed in 116 patients (91.3%), and 9 patients received neoadjuvant chemotherapy or radiochemotherapy, followed by complete resection. Two patients had diagnostic procedures only, followed by nonsurgical palliative treatment. The initial diagnosis in 5 patients of the neoadjuvant treatment group was SCLC. A clinical response to induction chemotherapy or radiochemotherapy was observed in 8 of the 9 patients (88.8%). One patient had stable disease.

The main surgical procedure was standard lobectomy in 88 patients (69.8%), sleeve lobectomy in 4 (3.2%), bilobectomy in 4 (3.2%), and pneumonectomy in 6 (4.8%). Sublobar resection was performed in 23 patients, comprising anatomic segmentectomy in 14 and wedge resection in 9. An extended resection was done in 5 patients, consisting of pericardium in 3 and chest wall in 2.

There were no intraoperative deaths. Bronchial-stump insufficiency developed in 1 patient who died at day 81 after multiple interventions; thus, the mortality rate was 0.8%. Complete resection (R0) was achieved in 99.2% and R1 resection in 1 patient with extended chest wall