Lung Cancer 81 (2013) 404–409

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

High grade neuroendocrine lung tumors: Pathological characteristics, surgical management and prognostic implications

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ARTICLE INFO

Article history:
Received 20 November 2012
Received in revised form 17 April 2013
Accepted 14 May 2013

Keywords:
Lung cancer
Large cell lung cancer
Neuroendocrine lung cancer
Surgery
Multimodality treatments

ABSTRACT

Among non-small cell lung cancers (NSCLC), large cell carcinoma (LCC) is credited of significant adverse prognosis. Its neuroendocrine subtype has even a poorer diagnosis, with long-term survival similar to small cell lung cancer (SCLC). Our purpose was to review the surgical characteristics of those tumors. The clinical records of patients who underwent surgery for lung cancer in two French centers from 1980 to 2009 were retrospectively reviewed. We more particularly focused on patients with LCC or with high grade neuroendocrine lung tumors. High grade neuroendocrine tumors were classified as pure large cell neuroendocrine carcinoma (pure LCNEC), NSCLC combined with LCNEC (combined LCNEC), and SCLC combined with LCNEC (combined SCLC). There were 470 LCC and 155 high grade neuroendocrine lung tumors, with no difference concerning gender, mean age, smoking habits. There were significantly more exploratory thoracotomies in LCC, and more frequent postoperative complications in high grade neuroendocrine lung tumors. Pathologic TNM and 5-year survival rates were similar, with 5-year ranging from 34.3% to 37.6% for high grade neuroendocrine lung tumors and LCC, respectively. Induction and adjuvant therapy were not associated with an improved prognosis. The subgroups of LCNEC (pure NE, combined NE) and combined SCLC behaved similarly, except visceral pleura invasion, which proved more frequent in combined NE and less frequent in combined SCLC. Survival analysis showed a trend toward a lower 5-year survival in case of combined SCLC.

Therefore, LCC, LCNEC and combined SCLC share the same poor prognosis, but surgical resection is associated with long-term survival in about one third of patients.

1. Introduction

Large cell carcinoma (LCC) accounts for approximately 9% of all lung cancers [1]. Its neuroendocrine histologic subtype, named large cell neuroendocrine carcinoma (LCNEC), has been described in 1991 [2], and accounts for one third of LCC [1]. LCNEC may harbor components of adenocarcinoma, squamous cell carcinoma, and other miscellaneous tumor cells. These cases are classified as combined LCNEC. Component may also include small cell carcinoma and in that case, tumors are classified as combined variants of small cell lung carcinoma (combined SCLC). Pure LCNEC, combined LCNEC, and combined SCLC are aggregated as high grade neuroendocrine lung tumors.

LCNEC are credited of having a significant adverse prognostic impact even in stage Ia, and LCNEC patients have been reported to have a worst survival than LCC patients [3]. Long-term survival may be as poor as in case of small cell carcinoma [1]. Our purpose was first to review the surgical characteristics and prognosis of patients with LCNEC as compared to LCC, and then to decipher the characteristics and prognosis associated with high grade neuroendocrine lung tumors.

2. Patients and methods

The clinical records of patients who underwent surgery for lung cancer from January 1980 to December 2009 in Georges Pompidou European Hospital (Paris) and Cedar Surgery Centre (Bois Guillaume) were retrospectively reviewed. The data were prospectively entered since April 1984. The preoperative workup included chest X-ray, bronchoscopy, computed tomography (CT) scan of the chest, spirometry, lung perfusion scan and a thorough search

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0169-5002/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2013.05.008

for distant metastases (including PET-scan in recent years). Mediastinoscopy was performed to exclude N3 disease and to confirm N2 involvement in patients included in various neoadjuvant treatment protocols depending on demand of different referring centers. N3 disease and distant metastases precluded surgery.

The staging system was the International Staging System for NSCLC recently modified [4]. We analyzed the pathology data and prognosis characteristics of these patients, focusing on LCC, pure LCNEC, and combined LCNEC. Following WHO recommendation and clinical practice, combined LCNEC and SCLC were classified as combined SCLC, but included in the study group for exhaustiveness [1]. Carcinoid tumors were excluded from the study as well as pure SCLC, but long term survival of the latter was considered for comparison. The study was approved by our Thoracic Surgery Society Ethic Committee (CERC-SFCTCV) that waived need for informed consent.

Follow-up information was obtained from the hospital case records, from a questionnaire completed by the chest physician or general practitioner, or from death certificates. The main outcome was the overall survival, defined as the time interval between the date of operation and the date of death or the last follow-up visit for censored patients. Mean follow-up duration was 73 ± 48 months. Survival curves were estimated by the Kaplan–Meier method. Statistical comparisons between survival distributions were made using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model for overall survival analysis. Univariate analysis used the following outcome variables: gender, age, type of surgical resection, histology, type of T and N involvement, and perioperative treatments. All data analyses were conducted with the two-sided test: a p value less than 0.05 was considered as statistically significant. The statistical software used for the analysis was SEM (Anticancer Centre Jean Perrin, Clermont-Ferrand, France) [5].

3. Results

3.1. Comparison between LCC and high grade neuroendocrine lung tumors

There were 625 patients, including 470 LCC (75%) and 155 high grade neuroendocrine lung tumors (25%). Patients' characteristics, management, and postoperative course are summarized in Table 1. There was no difference concerning gender, age, tobacco use, and induction treatments. There were more exploratory thoracotomies in LCC than in high grade neuroendocrine lung tumors. There was no difference regarding the type of surgical resection and its completeness. The rate of postoperative complications was significantly higher in high grade neuroendocrine lung tumors than in LCC patients, but the rate of postoperative mortality was not.

Pathologic or post-chemotherapy when applicable (pTNM or ypTNM, respectively) is shown in Table 1. The rate of yT0 was not different between both groups, but there was a trend toward a higher proportion of T1 and a lesser proportion of T2–T4 tumors in high grade neuroendocrine lung tumors, as compared to LCC. Otherwise the N status and the tumoral stage were similar between both groups.

Overall survival were not significantly different between groups: the median survival and 5-year survival rates were 27 months and 37.6% for LCC, versus 25 months and 34.3% for high grade neuroendocrine lung tumors, respectively ($p = 0.54$). This was also the case when only N0-patients were considered: in this case the median survival and 5-year survival rates were 62 months and 50% for LCC, versus 61 months and 50.4% for high grade neuroendocrine lung tumors, respectively.

Survival rates of high grade neuroendocrine lung tumors according to the administration of induction and adjuvant therapies are shown in Table 2. Induction-only patients received chemotherapy alone ($n = 10$) or in combination with radiation therapy ($n = 3$). Adjuvant-only patients received chemotherapy ($n = 20$), radiation therapy ($n = 14$), or a combination of both ($n = 19$). Such treatments were more frequently performed in advanced stages. Following first-line surgery, the stage distribution of patients without adjuvant treatment ($n = 73$) was stage I in 44 (60.3%), stage II in 14 (19.2%), stage III in 14 (19.2%), and stage IV in 1 (1.4%) patients. The stage distribution of patients with adjuvant treatment ($n = 53$) was stage I in 12 patients (22.6%), stage II in 17 patients ($n = 32.1\%$), stage III in 23 patients ($n = 43.4\%$), and stage IV in 1 (1.9%) patients ($p = 0.00052$).

3.2. Deciphering the subgroups of high grade neuroendocrine lung tumors

The subgroups of LCNEC, pure LCNEC ($n = 52$) are combined LCNEC ($n = 50$), are described in Table 3 together with LCNEC with SCLC component, classified as combined SCLC ($n = 53$). When comparing these 3 groups, the only difference concerned a higher rate of visceral pleura invasion in case of combined NE, despite the absence of difference in tumor size, emboli, and stages.

Among the combined LCNEC ($n = 50$), the association with adenocarcinoma was the most frequent and was found in 28 patients (56%). The type, stage and prognosis of combined LCNEC are reported in Table 4.

When comparing these 3 groups with a group of 73 patients operated for SCLC over the same period (Table 5), SCLC was associated with a significantly higher proportion of nodal extension, but a trend toward a lower 5-year survival.

4. Discussion

LCNEC of the lung is a pathologic entity initially characterized in the late 1980s by Hammond and Sause [6], Warren et al. [7] and Travis et al. [2]. Original criteria of diagnosis as defined by Travis were (i) a neuroendocrine appearance by light microscopy, including large cells with low nuclear-to-cytoplasmic ratio, coarse chromatin and frequent nucleoli, high mitotic rate, frequent necrosis and (ii) neuroendocrine features by immunohistochemistry or electron microscopy. LCNEC is only recognized since 1999 in the WHO classification of pulmonary tumors [1,8]. LCNEC with SCLC component is defined as combined SCLC. The term "High grade neuroendocrine lung tumor" aggregates pure LCNEC, combined LCNEC, and combined SCLC. We here present a large series of 155 high grade neuroendocrine lung tumors that may even be underestimated due to the absence of this entity in the old classifications. Takei et al. [9] retrospectively reviewed histologic characteristics of patients receiving an initial diagnosis of poorly differentiated non-small cell lung carcinoma ($n = 484$), SCLC ($n = 55$), carcinoid ($n = 31$), and LCNEC ($n = 12$) with immunohistochemistry confirming the neuroendocrine phenotype. A total of 87 patients were given a diagnosis of LCNEC after histologic review, which provided an indication on the frequency of this unrecognized diagnosis.

Most previous references to management of LCNEC as compared to LCC were published before the recent WHO classification, and do not refer to well classified neuroendocrine lung tumors. Several publications reporting series of LCNEC are shown in Table 6 [10–16]. All agreed about the poor prognosis of such a histology, but none studied high grade neuroendocrine lung tumors as a whole. Our reported 5-year survival rates of 37.6% for LCC and 34.3% for LCNEC are in the range of the previous published data. Battafarano et al. [17] reviewed 82 patients who underwent resection: overall 5-year