The Differences of Biological Behavior Based on the Clinicopathological Data Between Resectable Large-Cell Neuroendocrine Carcinoma and Small-Cell Lung Carcinoma

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Abstract

Few reports elucidated the biological differences between resectable large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). We reviewed the clinical data of 140 patients with resected high-grade neuroendocrine carcinomas (NECs) and analyzed the clinicopathological features in relation to their survival. We demonstrated there were no apparent differences in biological behavior between pure and combined subtypes in high-grade NEC, and there were significant differences in prognostic factors between LCNEC and SCLC.

Introduction: Large cell neuroendocrine carcinoma of the lung and SCLC are collectively classified as high-grade NECs. However, there have been few reports focusing on the differences of clinicopathological prognostic factors between resectable LCNEC and SCLC. **Patients and Methods:** We reviewed the clinical data of 140 patients who underwent complete resection of high grade NEC in our institute and analyzed the clinicopathological features in relation to their survival. **Results:** There were no statistically significant differences in overall and recurrence-free survival between pure and combined subtypes in either LCNEC or SCLC. In LCNEC, larger tumor diameter ($P = .01$), nodal metastasis ($P < .01$), lymphatic permeation ($P < .01$), and vascular invasion ($P = .01$) were unfavorable prognostic factors. However, in SCLC, tumor diameter and vascular invasion were not prognostic factors, but nodal metastasis ($P < .01$) and lymphatic permeation ($P = .03$) were strongly correlated with poor prognosis. **Conclusion:** There were no apparent differences in biological behavior between pure and combined subtypes in either LCNEC or SCLC. Lymphatic involvement was an important unfavorable prognostic factor in SCLC, whereas tumor diameter, vascular invasion, and lymphatic involvement had a poor prognostic effect in LCNEC.

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Introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung and small-cell lung carcinoma (SCLC) are collectively classified as high-grade neuroendocrine carcinomas (NECs) of the lung.[1-5] Since the histological entity of LCNEC was introduced in the World Health Organization (WHO) classification of 1999, the clinicopathological characteristics of LCNEC have been clarified, particularly with regard to patients' prognoses.[6-12] In contrast, SCLC is a common pulmonary neuroendocrine tumor, and patients with SCLC generally have very poor prognoses. Few reports have been published on the biological characteristics of resected SCLC, such as unfavorable prognostic factors, because surgical resection is indicated only for clinical stage I SCLC. Although the pathological diagnostic criteria of LCNEC have been established, it can be very difficult to distinguish between LCNEC and SCLC in some NECs. LCNEC shares many similarities with SCLC in histological, biological, molecular biological, and clinical aspects. The

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immunohistochemical and genetic similarities and differences between LCNEC and SCLC have been reported,[13] but the histopathological similarities and overlap in clinical characteristics have raised doubts over the distinction between LCNEC and SCLC, and led to proposals that the 2 types should be reclassified as a single group of high-grade NECs.[14,15]

High-grade NEC often includes other histological subtypes. When LCNEC has components of other non−small-cell lung cancer (NSCLC) types, it is classified as combined LCNEC. If LCNEC or other NSCLC components are included in SCLC, it is classified as combined SCLC. However the biological difference between pure and combined high-grade NECs have yet to be elucidated.

The aims of this study were to examine the biological differences between pure and combined high-grade NEC and to compare the difference of the clinicopathological prognostic features of resectable LCNEC and SCLC.

Patients and Methods

A total of 140 patients who underwent complete resection of high-grade NEC from January 1995 through December 2010 at the National Cancer Center Hospital East, Kashiwa, Japan, were enrolled in this retrospective study. All the patients had a solitary lesion, and patients who had received preoperative chemotherapy or thoracic radiotherapy were excluded. The preoperative evaluation included physical examination, blood chemistry analysis, bronchofiberscopy, chest radiography, computed tomography (CT) examinations of the chest, magnetic resonance imaging of the brain, bone scintigraphy, and positron emission tomography (PET), or combined PET-CT. If we needed to evaluate nodal metastasis, mediastinoscopy was performed. All patients underwent lobectomy or pneumonectomy and lymph node dissection. After surgery, SCLC patients were given adjuvant chemotherapy consisting of 4 cycles of cisplatin or carboplatin and etoposide when possible. For LCNEC patients, however, adjuvant chemotherapy was planned as in NSCLC patients. We surveyed the patients at 3-month intervals for the first 2 years and at 6-month intervals thereafter. The follow-up evaluation included physical examination, chest CT, and blood examination. Whenever any symptoms or signs of recurrence were detected, further evaluations were performed. We diagnosed recurrence on the basis of diagnostic imaging findings, and confirmed the diagnosis histologically when clinically feasible.

Data collection and analyses were approved and, because the research was a retrospective chart and specimen review and no personally identifiable information was included, the need to obtain written informed consent from each patient was waived by the institutional review board in March 2012.

We reviewed all the available pathology slides of resected specimens in this study. After fixing the specimens with 10% formalin and embedding them in paraffin, serial 4-μm sections were stained with hematoxylin and eosin. The sections were reviewed by 3 observers, who were blinded to patient identity. In some cases that were difficult to diagnose definitely, we consulted the other expert pathologists and a consensus diagnosis was reached. Formalin-fixed paraffin sections were stained for a panel of neuroendocrine markers, including a polyclonal antichromogranin A antibody (Ventana Medical Systems), CD56 (neural adhesion molecule) antibody (Nippon Kayaku), and monoclonal antisynaptophysin antibody (Dako), to confirm neuroendocrine features. Immunohistochemically, neuroendocrine differentiation was considered positive if the tumor cells exhibited focal, patchy, or diffuse staining in the intracellular areas for 1 or more of these 3 antibodies. We excluded large cell carcinomas with a neuroendocrine phenotype, which were negative on immunohistochemical staining but had neuroendocrine morphology, such as rosette formation and palisading. Pathological diagnoses were based on the criteria of the WHO guidelines.[16] Disease stages were classified according to the 7th edition of the Union for International Cancer Control tumor, node, metastasis classification system.[17]

The Fisher exact test was used to compare each categorical variable. Survival curves were plotted according to the Kaplan-Meier method and compared using the log-rank test. Overall survival (OS) was measured from the day of pulmonary resection to the date of death from any cause or the date on which the patient was last known to be alive. The recurrence-free survival (RFS) was measured as the interval between the date of resection and the date of recurrence diagnosis, or the date of death from any cause, or the latest date on which the patient was last known to be alive and disease-free, confirmed on the last CT before death. The Cox proportional hazards models were used to explore the effect of other clinicopathological factors to identify statistically independent prognostic factors. All tests were 2-sided, and P values $< .05$ were considered to be statistically significant. We used StatvView statistical software version 5.0 for Windows (SAS Institute Inc) for all statistical analyses.

Results

The study cohort included 119 men and 21 women, with a median age of 70 years (range, 22-85 years). The follow-up period for the patients in this study ranged from 2 to 133 months. The median follow-up time was 60 months (Table 1). Almost all the patients had a smoking history (138 patients; 99%). The median Brinkman Index was 1000 (range, 0-4160). The survival curves for the 140 patients with high-grade NEC according to the histological type are shown in Figure 1. Figure 1A shows the OS curves, and the 5-year OS rates of LCNEC and SCLC patients were 53.3% and 61.5%, respectively. There was no statistical difference in OS ($P = .30$). RFS curves are plotted in Figure 1B. The 5-year RFS rates of LCNEC and SCLC patients were 43.5% and 45.5%, respectively. There was no statistical difference in RFS ($P = .79$).

Of the 140 tumors, 59 tumors were diagnosed as SCLC. Of these, 43 were pure SCLC, and the remaining 16 were combined SCLC. Pure SCLC patients were younger than combined SCLC patients ($P = .04$). Tumor diameter was significantly larger in combined tumors ($P < .01$). There were no statistically significant differences in sex, smoking status, lymph node metastasis, lymphatic permeation, vascular invasion, or pleural invasion between pure and combined SCLC. The OS and RFS were not significantly different between the groups (OS, $P = .62$; 5-year OS, 63.2% vs. 58.8%; RFS, $P = .91$; 5-year RFS, 42.8% vs. 43.2%). Similar results were also observed when only data of stage I SCLC patients were analyzed (OS, $P = .64$; 5-year OS, 82.0% vs. 68.8%; RFS, $P = .51$; 5-year RFS, 58.6% vs. 68.8%).