

—Report on Experiments and Clinical Cases—

High Survival Rate of 6 Cases of Pulmonary Large Cell Neuroendocrine Carcinoma Formerly Classified as Small Cell Carcinoma

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Abstract

In the revised WHO classification of lung cancer, published in 1999, large cell neuroendocrine carcinoma (LCNEC) was employed as a new histological entity. LCNEC is generally considered a high-grade malignant lung cancer, and appropriate treatment remains to be determined. Before its new classification, LCNEC had long been classified into several entities. Advancing the review of previous cases in Nippon Medical School Hospital, we noticed that some LCNEC patients were formally diagnosed as having small cell lung cancer (SCLC), and they showed long-term survival.

Material and Methods: All histological specimens of surgically resected SCLC in Nippon Medical School Hospital were reclassified according to the 1999 WHO classification manual. Their neuroendocrine differentiations were confirmed by the use of immunostainings with chromogranin A and synaptophysin.

Results: Fourteen cases satisfied the qualifications for both histological and clinical reevaluation. Among them, 6 patients were reclassified as LCNEC, and their stage distribution was as follow : IA; 1, IB; 2, IIIA; 2, and IIIB; 1. Their survival term ranged from 33.8 to 78.0 months; 5 were still alive, and 1 (IIIB) died 57.6 months after surgery.

Discussion: According to this study, all the LCNEC patients who were treated as SCLC patients showed more favorable prognoses than patients described in published studies, even overall lung cancer. Therefore, it is suggested that multimodality therapy for SCLC may improve the prognoses of patients with LCNEC. (J Nippon Med 2001; 68: 335—339)

Key words: large cell neuroendocrine carcinoma, lung, multimodality therapy, small cell carcinoma

Introduction

In the revised WHO classification of lung cancer, published in 1999, large cell neuroendocrine carcinoma (LCNEC) was newly defined as a type of histological entity¹. Until that time, LCNEC was thought to

be categorized into several histological classifications such as poorly differentiated adenocarcinoma and atypical carcinoid²⁻⁴. Therefore, we questioned that which category pathologists employed LCNEC formerly. As we began to review cases in our hospitals, we noticed that some LCNECs were formerly diagnosed as small cell carcinoma (SCLC), and those

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patients showed long term survival.

There have been few survival analyses of patients with LCNEC. Travis et al. reported that the biological malignancy of LCNEC was not different from that of SCLC, saying the 5-year survival rate of LCNEC was 27%⁵. Jiang et al. showed that the survival rate of patients with LCNEC was significantly lower than that of patients with non-small-cell lung cancer³. These reports are based on operated cases and never mention the effectiveness of multimodality therapy including chemotherapy. No appropriate treatment for LCNEC has been established. Therefore, we analyzed the survival of patients with LCNEC in our hospital, especially focusing on LCNECs treated as SCLC using multimodality therapy. The purpose of this paper is to report cases of LCNEC treated by the use of multimodality therapy as SCLC, and it is expected to become a cornerstone for subsequent studies of treatment for patients with LCNEC.

Materials and Methods

Materials

All cases of surgically resected primary lung cancers that had been classified as SCLC in the medical records at Nippon Medical School Hospital between 1982 and 1999 were obtained. Initial diagnoses were produced in accordance with the General Rule for Clinical and Pathological Record of Lung Cancer of Japan current at the time of each diagnosis, which were modified versions of the former WHO classification^{6,7}. Twenty cases were recorded as SCLC. Among them, 14 cases were available for histologic reevaluation.

Methods

Histologic Reevaluation

Reviews of histological classification and TNM staging were carried out by 4 observers, 3 medical students (M.Y., S.T., and R.K.) and 1 pathologist (M.K.) with the use of all the slides of the 14 cases. Revised diagnoses were made and agreed to by all of the observers, according to the criteria of the 1999 WHO¹ and the 1997 UICC: TNM classification⁸. In some cases, additional sections of paraffin blocks were stained with alcian blue-periodic acid Schiff and/or mucicarmine stain to distinguish rosette structures and pseudoglandular structures from true glands and mucous secreting cells. Neuroendocrine differentiation was confirmed by the presence of positive immunohistochemical staining for chromogranin or synaptophysin. The first antibodies used were anti-chromogranin A (DAKO, Glostrup, Denmark) and anti-synaptophysin antibody (DAKO).

Survival Analysis

The type of operation and adjuvant therapy were documented by reviewing chart stored in the Departments of Surgery (II), Internal Medicine (IV), and the Division of Pathology of Nippon Medical School Hospital. Kaplan-Meier was used for survival analysis. In addition, the survival terms of patients with LCNEC in our results were compared with those in other literature, and special attention was paid to therapeutic details.

Results

Histologic Reevaluation (Table 1)

Among 14 cases which were available for histologic reevaluation, 8 had neuroendocrine morphology suspected as LCNEC. Immunohistochemistry showed that there were 6 cases of LCNEC (stained by chro-

Table 1 Reclassification of primary lung cancer formerly diagnosed as small cell carcinoma

Reclassified entity	n (n = 14 cases)
Large cell neuroendocrine carcinoma	6
Large cell carcinoma with neuroendocrine morphology	2
Small cell carcinoma	3
Combined small cell carcinoma	1
Squamous cell carcinoma; small cell variant	1
Poorly differentiated adenocarcinoma	1

mogranin A only, synaptophysin only, and both chromogranin A and synaptophysin: 2 cases, 1 case, and 3 cases, respectively). Two of the remaining 8 cases were negative for both neuroendocrine markers; therefore they were re-classified as large cell carcinoma with neuroendocrine morphology. The other 6 of the 14 cases were re-classified and confirmed as SCLC (3 cases), combined SCLC (SCLC and adenocarcinoma; 1 case), poorly differentiated adenocarcinoma (1 case), and small cell variant of squamous cell carcinoma (1 case).

Prognosis of the LCNEC Patients

Six cases of histologically confirmed LCNEC were distributed over 3 cases of stage I (IA; 1 case, IB; 2 cases) and 3 cases of stage III (IIIA; 2 cases, IIIB; 1 case), all of which were followed up more than 30 months (Table 2). The survival term of the patients ranged from 33.5 to 78.0 months. Fig. 1 demonstrates the survival curves. Five were ascertained to be still alive. One stage IIIB patient died of cancer 57.6 months after surgery.

Treatment of the LCNEC Patients

As this review of patients is retrospective, it entailed a wide variety of treatment approaches. Only one common characteristic treatment we should be aware of is that all of these cases were recognized and treated as SCLC, and multimodality therapy based on SCLC-type protocol was carried out (Table 2). Some information on one patient (the 70-year-old female in

Table 2) after discharge from Nippon Medical School Hospital was available only through personal communication, and we could not obtain detailed information about her chemotherapy. Three patients received multicyclic therapy: small dose combination of adriamycin, cisplatin, cyclophosphamide, mitomycin C, nimustine HCl, and vincristine.

Discussion

Before the concept of LCNEC was clearly established by WHO, pathologists classified LCNEC into several different categories (ex. atypical carcinoid, adenocarcinoma, undifferentiated carcinoma, and small cell carcinoma^{3,4,9}). Travis et al. evaluated appropriate criteria for LCNEC, and remarked that the most common interpathologists disagreement occurred between LCNEC and SCLC by prototype criteria of LCNEC⁹. Therefore, it is understandable that we found 6 cases of LCNEC among 14 patients formerly diagnosed as having SCLC.

A few reports have provided prognoses of patients with LCNEC. Travis et al. studied two hundred NE tumors, of which 37 were reclassified as LCNEC⁹. In that research, the 3-and 5-year survival rates of the patients with LCNEC were 35% and 9%, and the conclusion was that the survival rates of the patients with LCNEC were not significantly different from those with SCLC. Jiang et al. also reported that the 1-and 5-year survival rates for patients with surgically resected LCNEC were 58.8% and 44.8%, respectively³.

Table 2 Pathological stage, treatment, and outcome of large cell neuroendocrine carcinoma recorded as small cell carcinoma

Age	Sex	TNM	Stage	Operation	Adjuvant therapy	Status
70	F	T1N0	IA	LUL	NA	A (33.5M)
57	M	T2N0	IB	LUL	CDDP + VP16	A (63.6M)
67	F	T2N0	IB	RUL	Mult	A (78.0M)
60	M	T2N2	IIIA	RUL	CDDP + UFT, RT	A (47.8M)
67	M	T1N2	IIIA	RUL	Mult	A (59.7M)
67	M	T4N2	IIIB	LPN	Mult	D at 57.6M

Operation:

LUL=left upper lobectomy; RUL=right upper lobectomy; LPN=left pneumonectomy.

Adjuvant therapy:

NA=not available; CDDP=cisplatin; VP16=etoposide; Mult=multicyclic therapy; UFT=tegafur · urasil; RT=radiation.

Status: A=alive; D=dead.

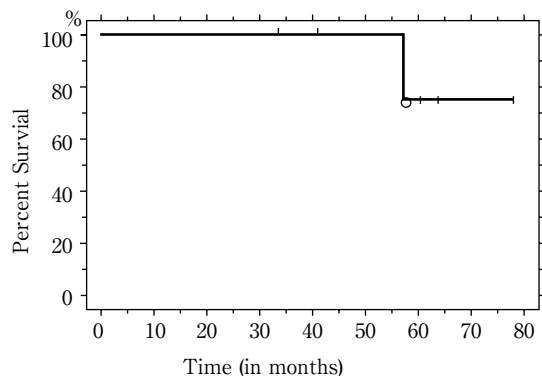


Fig. 1 Kaplan-Meier survival curve of 6 patients with large cell neuroendocrine carcinoma treated as small cell carcinoma

Our focus in this study is to seek appropriate treatment for LCNEC, but the pathological stage and details of treatment including adjuvant therapy were not clearly stated in either of the researches mentioned above. The survival term in our study showed that the prognoses are more favorable than those in the literature mentioned above³⁵. Moreover, the prognoses of the LCNEC patients in our study were relatively favorable compared with those of patients with overall primary lung cancer¹⁰⁻¹⁴. LCNEC was formerly classified into SCLC and non-small cell carcinoma (NSCLC), so it is certain that many LCNEC cases in the literature on prognosis had been treated as NSCLC, and that its therapeutic protocol may be different from that for SCLC. In our study, we limited the cases of LCNEC to those patients treated as SCLC cases, and to those who received surgical resection and adjuvant therapy. In this regard, our results suggest that the prognoses of LCNEC patients are improved by multimodality therapy based on SCLC-type protocol.

Contrary to this observation, Dresler et al. pointed out that there was no prolongation of survival or disease-free status in LCNEC patients who received adjuvant chemotherapy compared with those who did not⁴. However, they classified LCNEC before the WHO classification published in 1999¹, and they used their original criteria without using immunohistochemistry. Therefore, the LCNEC cases in the paper of Dresler et al. may include atypical carcinoid, LCNEC, combined LCNEC, large cell carcinoma (LCC), LCC with neuroendocrine morphology, LCC

with neuroendocrine differentiation, combined SCLC, undifferentiated carcinoma, and other histological types. This possibility is further supported by the results that the survival rate they showed was lower than that observed by Travis et al.⁵.

In the 1999 WHO classification, LCNEC was elected to continue to be separated from SCLC until it is proven that the chemotherapy used for SCLC is effective for patients with LCNEC¹. In this regard, the presented cases can be one of the examples to support the above hypothesis. However, our patients had favorable prognoses compared with those for SCLC patients. In contrast, a new study commented that LCNEC is resistant to the chemotherapy used for SCLC¹⁵. One possibility to solve the discrepancy between these researches is multimodality therapy including surgery. Therefore, it is emphasized that we need to continue to separate LCNEC from SCLC based on the hypothesis that LCNEC and SCLC have different biological behavior in terms of sensitivity to chemotherapy and metastatic ability. The number of LCNEC patients in our study is not sufficient for statistical analysis of survival, but the evidence we have suggests that surgery plus chemotherapy for SCLC is feasible for LCNEC. Recently, case reports of LCNEC treated with multimodality therapy have appeared^{16,17}. Therefore, we hope that further studies aimed at determining appropriate treatment for LCNEC will be carried out with considerations not only to differences in race and gene, but also to the interactions between different treatments, including the multimodality therapy that we have focused on.

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