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Results of surgical resection for patients with large cell carcinoma of the lung

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ABSTRACT

Purpose: The clinical features of large cell carcinoma (LCC) of the lung have remained unclear due to the low incidence of the disease. This study investigated the clinicopathological features and the surgical outcome in patients with LCC.

Subjects: This study clinicopathologically evaluated 975 patients who had undergone a resection for non-small cell carcinoma between 1994 and 2007. There were 57 (5.8%) patients with LCC among them.

Results: The LCC patients included 49 males and 8 females and included 9 patients with large cell neuroendocrine carcinoma. All patients excluding 1 had a smoking habit. The mean smoking pack-year index was 49.9 in the patients with LCC, 27.1 in 625 patients with adenocarcinoma, and 52.5 in 266 patients with squamous cell carcinoma, and this was significantly higher in the patients with LCC than in those with adenocarcinoma. The mean tumor diameter was 38 mm for LCC, 28 mm for adenocarcinoma, and 39 mm for squamous cell carcinoma. The pathological stage was IA in 11 patients, IB in 11, II in 12, IIIA in 16, IIIB in 5, and IV in 2. The post-operative 5-year survival rate was 60.5% for LCC, 64.3% for large cell neuroendocrine carcinoma, 67.0% for adenocarcinoma, and 50.1% for squamous cell carcinoma.

Conclusion: The tumor diameter was significantly larger for LCC than for adenocarcinoma at the time of diagnosis. The proportion of smokers and the smoking pack-year index in patients with LCC were significantly higher than those of adenocarcinoma. The surgical results were similar between LCC and other non-small cell lung carcinomas.

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1. Introduction

Lung cancer is among the most prevalent and lethal cancers worldwide, thus presenting 28% cancer death.^{1,2} Despite years of multidisciplinary management and research, the prognosis of patients with lung cancer remains dismal, and the 5-year survival rate in lung cancer is reported to be 10–15% throughout the world, because the vast majority present with inoperable advanced disease.³ Non-small cell lung cancer (NSCLC) accounts for 80% of all lung malignant tumor, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Large cell carcinoma (LCC) is classified as an undifferentiated bronchogenic carcinoma with no evidence of squamous or glandular maturation. In other words, it is an exclusion diagnosis made after ruling out adenocarcinoma, squamous cell carcinoma, and small cell carcinoma.⁴ The clinical features of LCC of the lung have remained unclear because the incidence is lower than 10%.

LCC is aggressive lung cancer, because of its rapid growth and early tendency to metastasize.⁵ The treatment of LCC is based on

the strategy for NSCLC. Therefore, chemotherapy is planned using the same regimen of NSCLC, except for large cell neuroendocrine carcinoma. Platinum-based chemotherapy is currently the standard treatment for LCC. However, LCC is frequently chemotherapy-refractory cancer like other NSCLCs.⁶ Surgical resection is also indicated for stage I–II disease as the first line treatment. Previous studies have suggested a dismal prognosis for large cell carcinoma, even after a curative resection, however, the prognosis remains poorly defined.^{5,7,8} The present study retrospectively investigated the clinicopathological features of LCC patients who underwent surgery.

2. Patients and methods

The hospital records of 975 consecutive patients who underwent a resection of non-small cell lung cancer between 1994 and 2007 were reviewed. The preoperative assessments included chest roentgenography, computed tomography (CT) of the chest, upper abdomen and brain. Clinical N2 status was defined by the presence of a lymph node more than 1 cm in a short axis diameter. Bone scintigraphy was performed to detect any bone metastasis. MRI (magnetic resonance imaging) of the brain was routinely employed

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after 2001. Bronchoscopy was routinely performed to obtain a pathological diagnosis by a transbronchial lung biopsy, and to evaluate endobronchial staging. The patients' records, including the clinical data, preoperative examination results, details of any surgical operations, histopathological findings and the TNM stages of all patients were also reviewed. The pulmonary function was evaluated using spirometry and arterial blood gas analysis. A ventilation-perfusion scan was routinely performed to predict post-operative lung function. Predictive post-operative lung function was considered as operable if the forced vital capacity (FVC) and forced expiratory volume in 1 s as percent of FVC (FEV_{1.0}) was greater than 900 ml/m² and 600 ml/m², respectively. All resected specimens, including the primary tumor and resected hilar and mediastinal lymph nodes, were examined to determine both the tumor histology and the extent of lymph node metastases. The histopathological findings were classified according to the World Health Organization criteria, and the UICC TNM staging system (6th edition) was employed.^{4,9} The definition of LCC is an undifferentiated non-small cell carcinoma that lacks the cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation. The pathological diagnosis was performed by 2 pathologists in each case.

Follow-up information was obtained from all patients through office visits or telephone interviews either with the patient, with a relative, or with their primary physicians. The patients were evaluated every 3 months by chest roentgenography, and chest CT scan and bone scintigraphy were obtained every 6 months for the first 2 years after surgery and annually thereafter. The mean observation time was 3.5-years.

The survival curve was calculated by the Kaplan–Meier method and compared using the Log-rank test for the univariate analysis. Categorical variables were compared by Fisher's exact test. The differences were considered to be significant if the *p* value was less than 0.05. The Statview V software program (Abacus Concept, Berkeley, CA) was used for all statistical analyses.

3. Results

There were 975 patients who underwent a resection for non-small cell lung cancer between 1994 and 2007, in the Second Department of Surgery, University of Occupational and Environmental Health. The current study evaluated 57 patients (5.8%) with LCC who had undergone lung resection. The 57 patients included 49 males and 8 females, indicating a significantly greater number of male patients (Table 1). The mean age of LCC patients was 67.4 years. All patients excluding 1 had a smoking habit. The average of smoking pack-year index was 49.9 in the patients with LCC, 27.1 in 625 patients with adenocarcinoma, and 52.5 in 266 patients with squamous cell carcinoma, and significantly higher in the patients with LCC than in those with adenocarcinoma (Table 2). The mean tumor diameter was 3.8 cm for LCC, 2.8 cm for adenocarcinoma, and 3.9 cm for squamous cell carcinoma, thus significantly longer for LCC than for adenocarcinoma (Table 3). Concerning the operative procedures, a pneumonectomy was performed in 2 patients, a lobectomy and bilobectomy in 51, and a segmentectomy in 4.

Nine of the 57 LCC patients were diagnosed to have large cell neuroendocrine carcinoma. The pathological stage of patients with LCC, excluding large cell neuroendocrine carcinoma, was IA in 8 patients, IB in 9, IIA in 2, IIB in 8, IIIA in 14, IIIB in 5, and IV in 2. The patients in stage IIIB included 3 patients with pulmonary metastasis in the same lobe of the primary tumor, and 2 patients with invasion of a great vessel (pulmonary artery or pulmonary vein) in the mediastinum. One of the patients at stage IV had pulmonary metastasis in the ipsilateral different lobe of the primary tumor, and the other patient had metastasis in the chest wall, which was

Table 1
Patient characteristics of large cell carcinoma.

	Large cell carcinoma <i>n</i> = 57	Non-small cell lung cancer except for large cell carcinoma <i>n</i> = 918
Average age	67.4	68.2
Male	49 (86.0%)*	613 (66.8%)
Female	8 (14.0%)	306 (33.3%)
Current and Ex Smoker	56 (98.2%)*	641 (69.8%)
Clinical stage		
IA	13 (22.8%)**	408 (44.4%)
IB	12 (21.1%)	212 (23.1%)
II	11 (19.3%)	94 (10.3%)
IIIA	15 (26.3%)	122 (13.3%)
IIIB	6 (10.5%)	54 (5.9%)
IV	0	28 (3.1%)
Operative procedure		
Pneumonectomy	2 (3.5%)	69 (7.5%)
Lobectomy bilobectomy	51 (89.5%)	729 (79.4%)
Segmentectomy	4 (7.0%)	56 (6.1%)
Partial resection	0	64 (7.0%)
Pathological stage		
IA	11 (19.3%)*	374 (40.7%)
IB	11 (19.3%)	170 (18.5%)
II	12 (21.1%)	105 (11.4%)
IIIA	16 (28.1%)	143 (15.6%)
IIIB	5 (8.8%)	88 (9.6%)
IV	2 (3.5%)	38 (4.1%)

p* < 0.01, *p* < 0.02.

resected with the primary tumor. The pathological stage of patients with large cell neuroendocrine carcinoma was IA in 3 patients, IB in 2, II in 2, and IIIA2 in 2. The post-operative 5-year survival rate was 61.5% for LCC, 67.0% for adenocarcinoma, and 50.1% for squamous cell carcinoma. Adenocarcinoma showed a significant better survival than squamous cell carcinoma (*p* < 0.05), however, there was no significant difference in the post-operative prognosis either between LCC and adenocarcinoma, or LCC and squamous cell carcinoma (Fig. 1). The 5-year survival rate of LCC except for large cell neuroendocrine carcinoma was 60.5%, and that of large cell neuroendocrine carcinoma was 64.3% (Fig. 2)

4. Discussion

NSCLC are classified into three major subgroups; adenocarcinoma, squamous cell carcinoma, LCC, and into several minor subgroups. The incidence of LCC is lower than 10%.⁴ The diagnosis of LCC is made by exclusion of other cell types of NSCLC and small cell carcinoma, and it is so-called the "wastebasket category".⁴ Therefore, preoperative diagnosis is sometimes difficult, because of the small amount of sample obtained in transbronchial lung biopsies. Larger surgical specimens often yield more information, and the diagnosis often changes to adenocarcinoma or squamous

Table 2
Comparison of the smoking index according to the histology.

	Large cell carcinoma <i>n</i> = 57	Adenocarcinoma <i>n</i> = 621	Squamous cell carcinoma <i>n</i> = 251
Smoking index (Pack-year)			
≤20	2 (3.5%)	313 (50.4%)	25 (10.0%)
20–40	19 (33.3%)	106 (17.1%)	61 (24.3%)
40–60	24 (42.1%)	137 (22.1%)	95 (37.8%)
60<	12 (21.1%)	65 (10.5%)	70 (27.9%)
Average of smoking index	49.9	27.1	52.5

**p* < 0.01 (Large cell carcinoma vs Adenocarcinoma).

Table 3
Comparison of the tumor size according to the histology.

	Large cell carcinoma n = 57	Adenocarcinoma n = 622	Squamous cell carcinoma n = 259
Maximum tumor size (cm)			
≤1	1 (1.8%)	58 (9.3%)	9 (3.5%)
1–2	14 (24.6%)	206 (33.1%)	35 (13.5%)
2–3	13 (22.8%)	155 (24.9%)	58 (22.4%)
3–4	9 (15.8%)	109 (17.5%)	52 (20.1%)
4–5	6 (10.5%)	39 (6.3%)	38 (14.7%)
5<	14 (24.5%)*	55 (8.8%)	67 (25.9%)
Average of tumor size (cm)	3.8*	2.8	3.9

* $p < 0.05$ (Large cell carcinoma vs Adenocarcinoma).

cell carcinoma. It is difficult to distinguish a poorly differentiated squamous cell carcinoma or adenocarcinoma preoperatively because of the indefinite diagnosis criteria.¹⁰

Large-scale surveys regarding the surgical results of the patients with lung cancer were conducted by the Japan Joint Committee of Lung Cancer Registry.^{11,12} These national surveillance data summarized 6644 and 13,010 patients that had undergone surgery in 1994 and 1999, respectively. They showed that the incidence of LCC was 3.6% in each investigation, suggesting LCC is a relatively rare subtype in Japan. According to these studies, the 5-year survival rate of LCC is 46.7% and 45.5%, respectively, and the prognosis of LCC is significantly poorer than that of adenocarcinoma. In the present study, the incidence of LCC was 5.8%, and the 5-year survival rate of LCC was 61.5%. The prognosis was unfavorable in comparison to adenocarcinoma, but not significantly. Therefore, the surgical treatment is performed with same indication according to other NSCLC, which is complete resection is the first line of treatment. Chemotherapy for LCC is administered according to the strategy of NSCLC. Cisplatin/pemetrexed significantly improved overall survival more than cisplatin/gemcitabine in patients with LCC (10.4 vs. 6.7 months, respectively; $p < 0.03$), suggesting that LCC should be considered together with adenocarcinoma (the non-squamous subgroup).^{6,13}

Smoking is known to have a strong association with the incidence of squamous cell carcinoma and small cell carcinoma in comparison to adenocarcinoma.^{14,15} However, LCC occurs predominantly in male and smokers.¹⁰ All patients excluding 1 were smokers, and the smoking pack-year index in patients with LCC were significantly higher than those of adenocarcinoma, in this study. Another clinical feature is a tendency of rapid and expansive tumor growth in

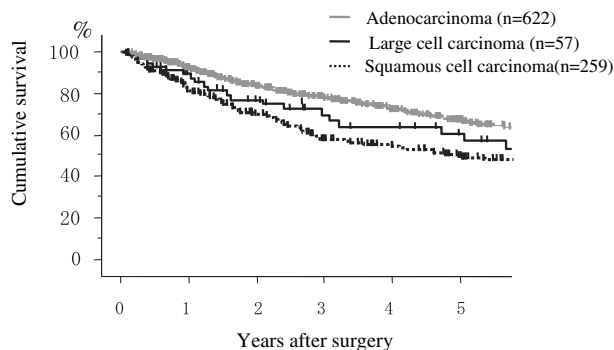


Fig. 1. Comparison of the overall survival curves according to the histology. The overall survival in each period was analyzed by the Kaplan–Meier method. The post-operative 5-year survival rates of adenocarcinoma, large cell carcinoma, and squamous cell carcinoma were 67.0%, 61.5, and 50.1%, respectively. The survival rate of adenocarcinoma was significantly better than that of squamous cell carcinoma ($p < 0.01$).

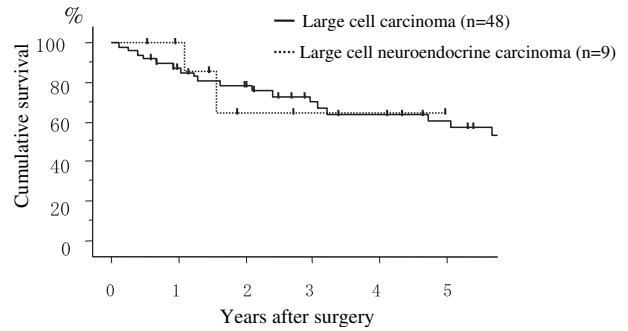


Fig. 2. Comparison of the overall survival curves between large cell carcinoma and large cell neuroendocrine carcinoma. The post-operative 5-year survival rates of large cell carcinoma, and large cell neuroendocrine carcinoma were 60.5% and 64.3%, respectively.

peripheral lung. LCC is reported to often form a large tumor mass at the time of diagnosis.^{5,10} The tumor is often accompanied by central necrosis.¹⁰ The tumor diameter was significantly longer for LCC than for adenocarcinoma, although tumor doubling time in these histology could not be evaluated in the present study.

LCC with neuroendocrine features was separated as a large cell neuroendocrine carcinoma the World Health Organization (WHO) in 1999.⁴ The histological features such as organoid nesting, trabecular, rosette-like and palisading patterns are confirmed by immunohistochemistry and electron microscopy. Although large cell neuroendocrine carcinoma is categorized as a variant of LCC, the biological behavior of large cell neuroendocrine carcinoma is similar to small cell carcinoma, indicating more aggressive clinical characteristics with an unfavorable prognosis.^{16,17} However, no difference was observed between LCC with or without neuroendocrine features in the present study. This may be an effect of the small series and low incidence of this subgroup (9 cases). Surgical treatment alone is not sufficient for large cell neuroendocrine carcinoma. Adjuvant chemotherapy with cisplatin/VP-16 as chemotherapeutic regimen similar to those for small cell lung cancer is effective for large cell neuroendocrine carcinoma.^{18,19} However, there have so far been only a few trials using chemotherapy or radiotherapy for LCC, because of its low incidence.

The post-operative prognosis of LCC was similar to that of other non-small cell lung carcinomas. A surgical resection is also recommended as the first line treatment for LCC with lung cancer. The present study suggests that LCC presents with a large mass at the time of diagnosis, and also has an association with higher smoking pack-year index.

Conflicts of interest

Not declared.

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Ethical approval

Reports describing data obtained from research conducted in human subjects must contain a statement in the Methods section indicating approval by the institutional review board and affirmation that informed consent was obtained from each patient.

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