Clinical response of large cell neuroendocrine carcinoma of the lung to perioperative adjuvant chemotherapy

Hisashi Saji[a], Masahiro Tsuboi[a], Jun Matsubayashi[b], Kuniharu Miyajima[a], Yoshihisa Shimada[a], Kentaro Imai[a], Yasubumi Kato[a], Jitsuo Usuda[a], Naohiro Kajiwara[a], Osamu Uchida[a], Tatsuo Ohira[a], Takashi Hirano[a], Kiyoshi Mukai[b], Harubumi Kato[a] and Norihiko Ikeda[a]

Patients with large cell neuroendocrine carcinoma (LCNEC) of the lung are considered to have poor prognosis. However, the benefit of adjuvant chemotherapy for these patients has not been established. In this study, we retrospectively evaluated the efficacy of perioperative chemotherapy for patients with completely resected LCNEC in a single-center setting. From 1999 through 2007, 45 patients with surgically resected LCNEC or mixed LCNEC containing at least one portion of the neuroendocrine differentiation or morphology in non-small cell lung carcinoma were enrolled as participants of this study. Survival rates were calculated by the Kaplan–Meier method. Differences between survival curves were computed with the log-rank test. For multivariate analysis, the Cox's proportional hazards regression model was used to evaluate variables that were significant predictors of survival. Of 1397 patients undergoing surgical resection for primary lung cancer from 1999 to 2007, 45 (3.2%) were classified as LCNEC. Thirty-six (80%) patients were men, and nine (20%) were women. Twenty-four (92%) of 26 patients were present or past smokers. Twenty-three (41%) of 45 patients received perioperative chemotherapy, including seven induction chemotherapies and 16 adjuvant chemotherapies. Survival of patients who underwent perioperative adjuvant chemotherapy was significantly higher than that of those who received surgery alone ($P=0.04$). The 5-year survival rate of patients who underwent perioperative adjuvant chemotherapy was 87.5%, whereas that of patients who underwent surgery alone was 58.5%. Even in stage I cases, perioperative adjuvant chemotherapy still favors survival compared with surgery alone. In the Cox proportional hazard multivariate analysis, surgery with or without chemotherapy showed an independent prognostic influence on overall survival ($P=0.0457$). Patients who received surgery alone were 9.5 times more likely to die than patients who underwent surgery plus chemotherapy. In conclusion, perioperative chemotherapy will be needed to improve survival in patients with LCNEC. As the population of LCNEC is small, it has been difficult to conduct randomized controlled trials to show the survival benefit of adjuvant chemotherapy. This should be, therefore, evaluated further in prospective multi-institutional phase II trials. *Anti-Cancer Drugs* **21:89–93 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Departments of [a]Thoracic Surgery and Oncology and [b]Pathology, Tokyo Medical University, Nishishinjuku, Shinjuku-ku, Tokyo, Japan

Correspondence to Dr Hisashi Saji, MD, PhD, Department of Thoracic Surgery and Oncology, Tokyo Medical Universtiy, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan
Tel: +81 3 3342 6111 x5845; fax: +81 3 3349 0326;
e-mail: saji-q@ya2.so-net.ne.jp

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Introduction

Pulmonary neuroendocrine tumors include a spectrum of four clinicopathological entities classified on the basis of the morphological and biological features: typical carcinoid and atypical carcinoid, which are tumors of low-grade and intermediate-grade malignancy, respectively, and large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC), which are considered to be high-grade malignancy tumors. Travis *et al.* [1] were the first to propose the term LCNEC in 1991. In 1999, the World Health Organization proposed a classification with rigorous histologic criteria for each subtype of LCNEC: (i) neuroendocrine morphologic features; (ii) high mitotic rate; (iii) necrosis; (iv) cytologic features of non-small cell lung carcinoma (NSCLC); and (v) positive immunohistochemical staining for one or more neuroendocrine markers [2].

LCNEC of the lung represents approximately 2–3% of lung malignancies and is known for its poor prognosis [3–10]. A recent large sample study from Japan, which was conducted in a retrospective, multi-institutional setting, including a critical review of histology by an expert panel, apparently showed that no prognostic difference was noted between LCNEC and SCLC [11]. Now, it is recognized that high-grade neuroendocrine histology uniformly indicated poor prognosis regardless of its histologic type. Considering the necessity of adjuvant

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therapy for LCNEC, this preliminary study was conducted to evaluate the efficacy of perioperative adjuvant chemotherapy in a retrospective single-center setting.

Patients and methods

Patients and pathological review

Of 1397 patients who underwent surgical resection for primary lung cancer from 1999 to 2007 at Tokyo Medical University, 45 (3.2%) patients with the histological characteristics of LCNEC were enrolled as participants of this study. According to the histological typing of lung and pleural tumors in the World Health Organization International Histological Classification of Tumors, 3rd edition [2], LCNEC is classified as a variant of large cell carcinoma (LCC). In this schema, LCCs are classified into four types: pure LCNEC, LCC with neuroendocrine differentiation, LCC with neuroendocrine morphology, and classic LCC. As earlier studies reported that NSCLC with neuroendocrine features have similar prognosis to that of pure LCNEC [3,12–14], in this study, LCNEC, including pure LCNEC and mixed LCNEC, in which at least one portion of the neuroendocrine differentiation or morphology in NSCLC, were enrolled.

Neuroendocrine morphology includes the following features: (i) neuroendocrine morphology, such as organoid nesting, nuclear palisading, rosettes, and trabecular pattern; (ii) a high mitotic rate of at least 11 per 2 mm^2 (10 high-power fields); (iii) necrosis (often large zone); and (iv) cytologic features of NSCLC, including large cell size, low nuclear-to-cytoplasm volume ratio, vesicular or fine chromatin, or frequent nucleoli, or a combination of these. Immunohistochemical analysis was performed to confirm the neuroendocrine differentiation of the tumors. For this purpose, formalin-fixed paraffin sections were stained for a panel of neuroendocrine markers, including chromogranin A (1 : 1500; Dako, Tokyo, Japan), synaptophysin (1 : 100; Dako), and neural cell adhesion molecule (1 : 50; Dako), using standard methods. Immunohistochemically, the tumor was considered as positive if the tumor cells exhibited focal, patchy, or diffuse staining in the intracellular locations for each antigen. Histological specimens were diagnosed by experienced pathologists (K.M. and J.M.) at the Department of Pathology, Tokyo Medical University.

Clinical findings and statistical analysis

Clinical information about the cases was obtained from the medical records. The final pathological staging was assigned according to the International Union Against Cancer TNM classification system [15]. Follow-up information was completely acquired within the last 6 months for all the patients. The survival time was measured from the date of first treatment, including operation or induction chemotherapy. All statistical analyses were performed with the StatView software package (StatView 5.0; SAS Institute Inc., Cary, North Carolina, USA). Survival rates were calculated by the Kaplan–Meier method. Differences between survival curves were computed with the log-rank test. For multivariate analysis, the Cox's proportional hazards regression model was used to evaluate variables that were significant predictors of survival. In all statistical analyses, significance was defined as a P value of less than 0.05.

Results

Patient demographics

Of 1397 patients undergoing surgical resection for primary lung cancer from 1999 to 2007, 45 (3.2%) were classified as LCNEC, including pure LCNEC, LCC with neuroendocrine differentiation, LCC with neuroendocrine morphology, and mixed LCNEC. Of these, only 7 (15%) were diagnosed as LCNEC before surgery, nine as poorly differentiated adenocarcinoma, two as poorly differentiated squamous cell carcinoma, one as LCC, four as NSCLC, three as SCLC, and one as adenosquamous cell carcinoma.

The clinicopathological profiles of the cases are summarized in Table 1. The median age of the patients was 65 years (range, 40–83 years). Thirty-six (80%) patients were men, and nine (20%) were women. Twenty-four (92%) of 26 patients were present or past smokers in the clinical chart. Operative procedures performed included 40 (90%) lobectomies, three (6%) wedge resections, and two (4%) pneumonectomies. The distribution of pathological stage was 11 (25%) stage IA, 16 (36%) stage IB, 5 (11%) stage IIA, 3 (6%) stage IIB, 7 (16%) stage IIIA, and 2 (4%) stage IIIB.

Twenty-three (41%) of 45 patients received perioperative chemotherapy, including seven induction chemotherapies and 16 adjuvant chemotherapies. The regimens of these chemotherapies are listed in Table 2. Of these, 21 (91%) patients had received platinum-based chemotherapy before or after surgery.

Survival in all stages

Survival data were collected for each patient from the data of operation or first chemotherapy, with a median

Table 1 Clinicopathological profiles of 45 surgically resected LCNEC cases

Mean age, range (years)	66.4 (40–83)
Sex, *n* (%)	
Men	36 (80)
Women	9 (20)
Present and past smoking, *n* (%)	24/26 (92)
Pathological staging (%)	
IA	11 (25)
IB	16 (36)
IIA	5 (11)
IIB	3 (6)
IIIA	7 (16)
IIIB	3 (6)
Surgical procedure, *n* (%)	
Wedge resection	3 (6)
Lobectomy	40 (90) (bilobectomy, three cases)
Pneumonectomy	2 (4)

LCNEC, large cell neuroendocrine carcinoma.

Table 2 Regimens of perioperative chemotherapy

Induction chemotherapy, *n* (%)	7 (13)
CBDCA + PTX	4
CDDP + CPT-11	3
Adjuvant chemotherapy, *n* (%)	16 (28)
CBDCA + PTX	5
UFT	2
CDDP + VP-16	2
CDDP + CPT-11	2
CBDCA + CPT-11	4
CBDCA + DTX	1
Surgery alone, *n* (%)	22 (59)

CBDCA, carboplatin; CDDP, cisplatin; CPT-11, topotecan; DTX, docetaxel; PTX, paclitaxel; UFT, uracil and tegafur; VP-16, etopocide.

follow-up of 31 months, because recent cases were enrolled and analyzed. As shown in Fig. 1, the 2 and 5-year overall survival for the entire group was 89.2 and 69.4%, respectively (40.3% 5-year survival reported by Asamura *et al.* [11]) (Table 3). Survival of patients who underwent perioperative adjuvant chemotherapy was significantly higher than that of those who underwent surgery alone ($P = 0.04$) (Fig. 2). The 5-year survival rate of patients who underwent perioperative adjuvant chemotherapy was 87.5%, whereas that of patients who underwent surgery alone was 58.5% (88.9% 5-year survival reported by Iyoda *et al.* [16]) (Table 3). There was no significant difference in clinicopathological factor, including age, sex, pathological staging, and surgical procedure between perioperative adjuvant chemotherapy group, and surgery alone group (data not shown).

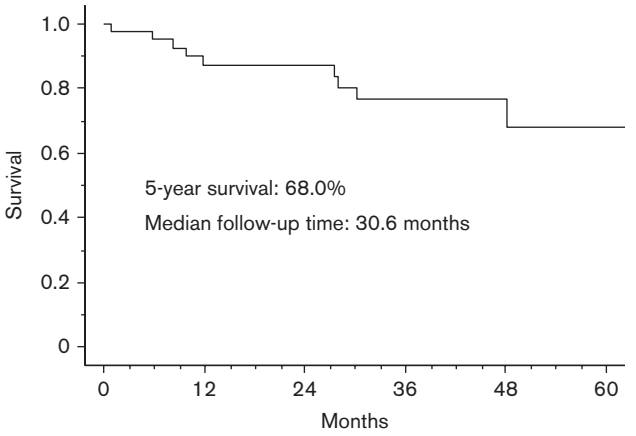
Survival in stage I

Figure 3 shows a comparison of survival between LCENC ($n = 27$) and NSCLC ($n = 774$) in early-stage lung cancer patients who underwent surgery during the same period. Prognosis is significantly worse in stage I patients with LCNEC than in those with NSCLC (65.4 vs. 84.5%, $P = 0.0067$). Interestingly, survival benefit of perioperative adjuvant chemotherapy can be observed even in the stage I LCNEC cases as well as in all stage cases (Fig. 4).

Multivariate analysis of survival benefit

The association of sex, age, pathological staging, and surgery with or without chemotherapy with survival was analyzed by the Cox proportional hazard multivariate analysis. As shown in Table 4, surgery with or without chemotherapy showed an independent prognostic influence on overall survival ($P = 0.0457$). Patients who underwent surgery alone were 9.5 times more likely to die during the follow-up period than were patients who underwent surgery plus chemotherapy.

Fig. 1



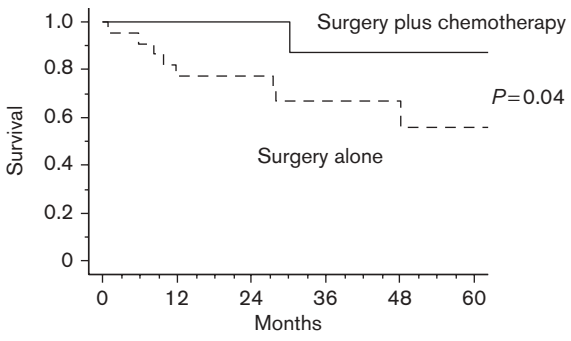
Overall survival of 45 surgically resected large cell neuroendocrine carcinoma cases.

Table 3 Five-year survival rate of LCNEC in the literature

Study	Number of cases	5-year survival rate (%)
Iyoda *et al.* [16]	15	88.9 (adjuvant chemotherapy)
Veronesi *et al.* [10]	144	42.5
Asamura *et al.* [11]	141	40.3
Battafarano *et al.* [9]	45	30.2
Doddoli *et al.* [7]	123	36.0
Paci *et al.* [6]	48	21.2
Zacharias *et al.* [14]	20	47.0
Takei *et al.* [5]	87	57.0
Iyoda *et al.* [16]	50	Approximately 35[a]
Garcia-Yuste *et al.* [17]	22	21
Travis *et al.* [4]	37	27.0

LCNEC, large cell neuroendocrine carcinoma.
[a]Number estimated from survival curve.

Fig. 2

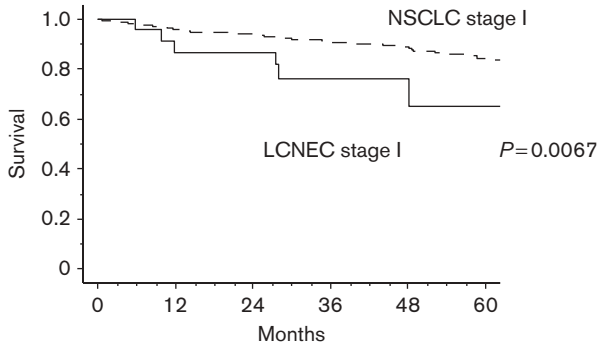


Overall survival of patients in surgery plus chemotherapy [$n = 23$ (87.5%)] and surgery-alone groups [$n = 22$ (55.8%)].

Discussion

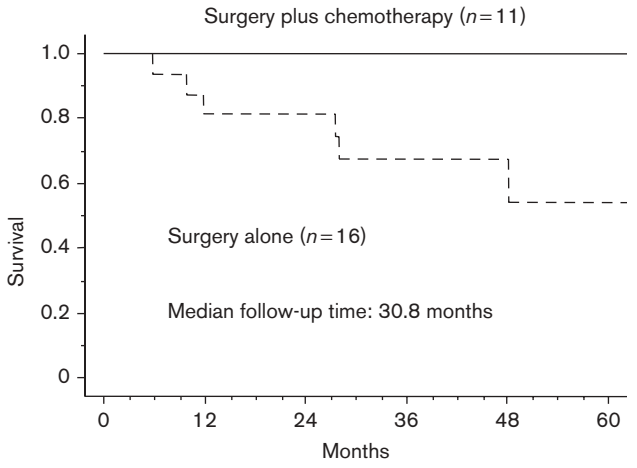
LCNEC of the lung was initially characterized by Travis *et al.* [1] in 1991, forming a separate category of neuroendocrine tumors of the lung. In 1999, the WHO proposed a new classification of pulmonary neuroendocrine tumors. As surgical resection of LCNEC in many series has been described with 5-year actuarial survival that is far worse than that reported for other histologic variants of NSCLC [4–7,9–12,14,17], considerable debate has emerged as to whether these tumors should be classified and treated as NSCLC or SCLC. Efforts to

Fig. 3



Overall survival of non-small cell lung carcinoma (NSCLC) [$n=774$ (84.5%)] and large cell neuroendocrine carcinoma (LCNEC) [$n=27$ (65.4%)] in stage I cases.

Fig. 4



Overall survival of surgery plus chemotherapy ($n=11$) and surgery-alone groups ($n=16$) in stage I large cell neuroendocrine carcinoma cases.

Table 4 Results of multivariate analysis of prognostic factors influencing survival of patients with LCNEC after treatment

Clinical factors	HR (95% CI)	*P* value
Treatment		
Surgery alone/surgery plus chemotherapy	9.472 (1.050–85.478)	0.0457[a]
Sex		
Women/men	1.400 (0.272–7.203)	0.7668
Age		
70 years and more/less than 70 years	0.491 (0.135–1.789)	0.2812
Staging		
I/II, III	0.807 (0.196–3.325)	0.7668

CI, confidence interval; HR, hazard ratio; LCNEC, large cell neuroendocrine carcinoma.
[a]Statistically significant.

identify effective adjuvant therapies might be useful in improving treatment outcomes with this aggressive type of lung cancer.

The incidence of LCNEC in our series of resected lung cancers was 2.3%, and this figure is in agreement with other series reported earlier. In addition, the mean age of patients treated for LCNEC ranged from 40 to 83 years of age, with a mean of 65 years and the predominant patients with LCNEC were men (80%) and/or smokers (92%). The overall 5-year survival for patients with LCNEC treated with surgical resection with or without chemotherapy was 68.0%, which was relatively better than that reported in earlier studies except for one study reported by Iyoda *et al.* [16] as shown in Table 3. The reason of this relatively good prognosis is that recent cases were enrolled in our study and nearly 40% of our cases received chemotherapy before or after surgery.

In an effort to improve cure rates of LCNEC patients, postoperative adjuvant chemotherapy or radiotherapy has been used in several studies. Unfortunately, no study has yet reported a definitive survival benefit of postoperative adjuvant therapy in LCNEC patients. Rossi *et al.* recently reported that adjuvant chemotherapy based on CDDP plus VP-16 was effective for patients with LCNEC [18]. As reported earlier, we also show the survival benefit of perioperative adjuvant chemotherapy for resected LCNEC in our current series. Moreover, to the best of our knowledge, this is the first report to show that the survival benefit can be observed even in stage I cases. In general, it is already known that adjuvant chemotherapy is indicated and its survival benefit is proved in stage II or III NSCLC [19–23]. However, there is no clinical trial that has shown survival benefit of adjuvant chemotherapy in stage I NSCLC. We showed the possibility of survival benefit in stage I LCNEC in this series. Our studies were conducted in retrospective cohort and were not followed in enough periods. Therefore, prospective pooling experience from multicenter to reach a large number of cases is warranted to give additional information on the impact of perioperative chemotherapy on stage I LCNEC.

As a result of high expression of the multidrug resistance gene (*MDR1*) in LCNEC, it has been suspected that LCNEC is resistant to conventional chemotherapy for NSCLC. Yamazaki *et al.* [24] reported on the clinical response of a series of 20 cases of LCNEC to chemotherapy suggesting that the response rate of LCNEC to cisplatin-based chemotherapy was comparable with that of SCLC, with a response rate of 50% for one complete response. Hiroshima *et al.* [25] postulated that chemotherapy might be as effective for LCNEC as for SCLC, because the genetic profile of LCNEC is similar to that of SCLC. The expression of p53, Ki-67, K-ras, and C-raf-1 in LCNEC is genetically and immunohistochemically more similar to that in SCLC

than in NSCLC [26,27]. Although Iyoda *et al.* [16] reported a small-sized phase II study of 15 patients with LCNEC, they were the first to report and establish the benefit of adjuvant chemotherapy for patients with completely resected LCNEC in a prospective phase II study setting, and a regimen of adjuvant chemotherapy consisting of cisplatin and VP-16, which is one of the standard regimens for SCLC, which seems promising for the improvement of the prognosis of patients with completely resected LCNEC. In addition, in our series, all the patients who underwent surgery plus perioperative chemotherapy received platinum-based chemotherapy except for two receiving UFT (a combination of uracil and tegafur) as adjuvant chemotherapy. Moreover, 14 of 23 cases (60%) in this group received platinum-based chemotherapy, including VP-16 or CPT-11, which is one of the standard regimens for SCLC. Survival analysis, including the Kaplan–Meier method and multivariate analysis using the Cox's proportional hazards regression model, showed that perioperative chemotherapy could improve the survival for patients with resected LCNEC. Moreover, even in our series with stage I disease, prognosis is significantly worse in LCNEC than in NSCLC. Therefore, adjuvant chemotherapy for stage I LCNEC might also be considered.

Conclusion

In conclusion, LCNEC of the lung is an uncommon but aggressive lung cancer associated with a poor prognosis, even in patients with stage I disease. Perioperative chemotherapy, in particular using a regimen for SCLC, such as platinum plus VP-16 or CPT-11, will be needed to improve survival in patients with resected LCNEC. As the population of LCNEC is small, it has been difficult to conduct randomized controlled trials to show the survival benefit of adjuvant chemotherapy. This should, therefore, be evaluated further in multi-institutional phase II trials.

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