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ORIGINAL REPORT

Neuroendocrine Neoplasms of the Lung: A Prognostic Spectrum

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ABSTRACT

Purpose
Neuroendocrine (NE) tumors of the lung include typical carcinoid (TC), atypical carcinoid (AC), large-cell NE carcinoma (LCNEC), and small-cell lung carcinoma (SCLC). Their clinicopathologic profiles and relative grade of malignancy have not been defined.

Patients and Methods
From 10 Japanese institutes, 383 surgically resected pulmonary NE tumors were collected. The histologic diagnosis was determined by the consensus of a pathology panel consisting of six expert pathologists as TC, AC, LCNEC, or SCLC on the basis of the WHO classification, and its relationship to clinicopathologic profiles was analyzed.

Results
Of the 383 tumors, 18 were excluded because of an improper specimen. The pathology panel reviewed the remaining 366 tumors, and a diagnosis of NE tumor was made in 318 patients (87.4%); 55 patients had TC, nine had AC, 141 had LCNEC, and 113 had SCLC. The 5-year survival rates of patients with all stages were as follows: 96.2% for TC, 77.8% for AC, 40.3% for LCNEC, and 35.7% for SCLC. There was significant prognostic difference between TC and AC as well as between AC and LCNEC+SCLC. However, there was no difference between LCNEC and SCLC, and their survival curves were superimposed. The multivariate analysis indicated that histologic type, completeness of resection, symptoms, nodal involvement, and age were significantly prognostic.

Conclusion
The grade of malignancy of NE tumors was upgraded in the following order: TC, AC, LCNEC, and SCLC. No prognostic difference was noted between LCNEC and SCLC. The high-grade NE histology uniformly indicated poor prognosis regardless of its histologic type.

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INTRODUCTION

Normal lung contains a population of neuroendocrine cells, where the term neuroendocrine (NE) defines a specific group of cells based on their secretory products, distinct staining characteristics, and ability to uptake and decarboxylate amine precursors.[1] Lung tumors originating from NE cells or differentiating into NE cells have been recognized, and they are represented by a wide range of pathologic entities.[2-5] It is now widely recognized that NE tumors of the lung include a spectrum, from low-grade typical carcinoid (TC) to intermediate-grade atypical carcinoid (AC) to high-grade large-cell NE carcinoma (LCNEC) and small-cell lung carcinoma (SCLC).[2-5] LCNEC is a unique tumor that shows immunohistochemical and morphologic appearance as high-grade NE tumors and non–small-cell nuclear features. Its clinicopathologic behaviors have been elucidated only recently.[5-12]

In the recent revision of the WHO classification of lung and pleural tumors, the same grading was adopted with detailed criteria for each subtype of NE tumors, although LCNEC was subcategorized as a type of large-cell carcinoma.[13] However, the important issues regarding NE tumors of the lung have not yet been defined. In particular, the grade of malignancy of each NE subtype has not been defined. There is little information available on the relative grade of malignancy among the several histologic types. However, to ensure the appropriate choice of treatment strategy for patients with various types of NE lung tumors, a histology-specific understanding of clinicopathologic behavior and prognosis is indispensable.

Considering the importance of histologic diagnoses and their reproducibility, this study was conducted in a retrospective, multi-institutional setting with a critical review of histology by an expert panel. The clinicopathologic background

of patients was collected, and histology-specific characteristics were extensively analyzed.

PATIENTS AND METHODS

Patients

A total of 383 patients with a histologic diagnosis of primary pulmonary NE tumor at each institution were enrolled onto this retrospective study. Intermediate- and high-grade NE tumors were a focus for enrollment. Samples were obtained from 10 institutions in the Japanese Multicenter Study Group of NE Tumors (Appendix). To ensure that there would be enough specimens for pathologic examination, only surgical cases were considered. Patients who were diagnosed only by biopsy sample and treated by some modality other than surgery were excluded. Histopathologic and clinicopathologic studies were performed. The final histologic diagnosis was established by an expert central review, as described later in detail. Extensive clinical information was also collected and included demographic data, surgical information, preoperative serum tumor marker levels, pathologic data, endocrine syndromes (Cushing's syndrome, acromegaly, and so on), tumor recurrence, and survival. For serum tumor markers, three markers, carcinoembryonic antigen (CEA; normal range, < 5 ng/mL), neuron-specific enolase (NSE; normal range, < 15 ng/mL), and progastrin-releasing peptide (proGRP; normal range, < 46 ng/mL), were studied. All patients were staged postsurgically according to the International Union Against Cancer TNM classification system.[13]

Pathologic Diagnosis: Central Review

To ensure an accurate histologic diagnosis as NE tumor, the histology of all of the enrolled patients was reviewed by a pathology panel consisting of six experts (T.K., Y.M., T.I., Y.I., M.N., and T.Y.). Paraffin-embedded blocks or unstained slide glasses were obtained in all cases and processed by routine hematoxylin and eosin staining and immunohistochemical studies solely at one institution (T.K. and S.-X.J.). To demonstrate the NE phenotype, at least three antibodies to chromogranin-A, CD56 (neural adhesion molecule), and synaptophysin were used. Immunohistochemically, the tumor was considered as positive if the tumor cells exhibited focal, patchy, or diffuse staining in the intracellular locations for each antigen. The classification criteria were based on the revised WHO classification of lung carcinoma (1999),[14] in which TC, AC, LCNEC, and SCLC are strictly differentiated. The process of central review was as follows. First, the pathology panel members performed a pathology review independently, and their respective reports were sent directly to the central office. After the individual reviews were completed, a review meeting was held to establish a final consensus on the histologic type in each case. The evaluation of immunohistochemical staining was also documented.

Statistics

The Kaplan-Meier product limit estimator was used to graphically display the survival curves, and the log-rank test was used to compare survival between different groups. The Cox proportional hazard model was used to examine the effects of variables that may have affected the prognosis of patients with NE tumors. $P \leq .05$ was considered significant.

RESULTS

Among the 383 patients enrolled, 18 were excluded from the study. In 17 patients, the specimens were judged to be inappropriate because either the tumors were of nonpulmonary origin or no specimens were available from the primary site. In one patient, the eligibility criteria were not met because this was an autopsy case. The remaining 365 tumors were considered for further central pathology review.

Central Pathology Review

Of the 365 tumors, as a final agreement of the review meetings, a total of 318 (87.1%) were diagnosed as pulmonary NE tumors, whereas a histology of non-NE tumor was confirmed in 47 tumors (12.9%; Table 1). Actually, the pathology panel could not reach a consensus with regard to the histologic type of 14 high-grade NE tumors at the initial session of panel meetings. Therefore, after enough intervals, the panel meetings were held again, and the final consensus as either LCNEC or SCLC was established. Of the NE tumors, a diagnosis of TC, AC, LCNEC, and SCLC was made in 55, nine, 141, and 113 patients, respectively. In the non-NE tumors, large-cell carcinoma (LCC) was most commonly seen (33 patients), followed by poorly differentiated squamous cell carcinoma (seven patients), poorly differentiated adenocarcinoma (three patients), pulmonary blastoma (two patients), and indeterminate histology by treatment (two patients). When looking at the histologic subtypes of 74 LCCs, 141 were diagnosed as LCNEC because of the coexistence of NE morphology and phenotype. However, the NE phenotype was not demonstrated despite the presence of NE morphology in 11 patients (LCC with NE morphology), and the NE morphology was not demonstrated despite the presence of NE phenotype in 12 patients (LCC with NE phenotype). In the remaining 10 patients, neither NE phenotype nor NE morphology was demonstrated (LCC). Among 141 LCNECs, 15 tumors (10.6%) were combined with other histologic types, and 126 tumors (89.l4%) were not combined (Table 2). Also, among 113 SCLCs, 30 tumors (26.6%) were combined with other histologic types, and 83 tumors (73.4%) were not combined (Table 3). Despite the various combinations of high-grade NE tumors with other histologic types, neither TC nor AC was seen as the combined histology for LCNEC and SCLC.

Clinicopathologic Profiles

The clinical background and profiles were studied according to the histologic type (Table 4). Aggressive tumors tended to affect older patients. In particular, patients with TC were significantly younger than patients with other tumor histologies. A remarkable difference in sex distribution was seen between carcinoid tumors (TC and AC) and other high-grade NE carcinomas (LCNEC and SCLC). Compared with carcinoid tumors, the high-grade NE tumors affected men significantly more often than women, with males accounting for more than 80% to 90% of the tumors. Also, 95% to 100% of the patients with high-grade NE carcinomas had a smoking history, whereas only half of the patients with carcinoid tumors were smokers. Only four patients (1.3%) in the entire group of patients with NE tumors showed

Table 1. Histologic Diagnosis

Histologic Type	No. of Patients	%
NE tumors	318	87.1
TC	55	15.1
AC	9	2.5
LCNEC	141	38.6
SCLC	113	31.0
Non-NE tumors	47	12.9
LCC	33	9.0
Others	14	3.8
Total	365	100

Abbreviations: NE, neuroendocrine; TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma; LCC, large-cell carcinoma.

Table 2. Details of Histologic Diagnosis of LCNEC

Histologic Type	No. of Patients	%
LCNEC, not combined	126	89.4
LCNEC, combined	15	10.6
With AD	5	3.5
With SQ	8	5.7
With others	2	1.4
Total	141	100

Abbreviations: LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma; AD, adenocarcinoma; SQ, squamous-cell carcinoma.

symptoms related to the paraneoplastic syndromes. The following syndromes were seen: Eaton-Lambert's syndrome in two patients with SCLC, syndrome of inappropriate antidiuretic hormone secretion in one patient with SCLC, and carcinoid syndrome in one patient with TC. In AC and LCNEC, paraneoplastic syndrome was not seen. The serum tumor markers of CEA, NSE, and proGRP were measured before surgery in 298 (93.7%), 240 (75.5%), and 79 (24.8%) of 318 patients, respectively (Table 5). The serum CEA level was elevated in half of the patients with LCNEC or SCLC. Although proGRP was a good marker of high-grade NE tumors, the elevation of NSE level was limited in these patients, probably because of the relatively early stage for the tumors. The pathologic profiles of resected tumors are listed in Table 6. The average size of LCNEC (41 mm) was the largest among NE tumors; other types averaged approximately 30 mm in diameter. In TC, nodal involvement was seen in only two patients (3.6%), whereas approximately half of the patients with other histologic types had lymph node involvement in both the pulmonary hilum and mediastinum. Accordingly, the postsurgical stage of TC was stage I in more than 90% of the patients. However, approximately half of the patients with the other types of tumors were categorized as stage I, and there was no remarkable difference in the stage distribution between the different histologic types.

Prognosis

The follow-up for the patients in this study ranged from 2 to 197 months. The median follow-up time was 60 months. There were 124 tumor recurrences (39.0%) among all of the patients with NE tumors (Table 7). Compared with carcinoid tumors, high-grade NE tumors had a higher recurrence rate, at appproximately 50%. The survival curves for the 318 patients with NE tumors according to the histologic type are shown in Figure 1. The 5-year survival rates for patients with TC, AC, LCNEC, and SCLC were 96.2%, 77.8%, 40.3%, and 35.7%, respectively. The histologic type as NE tumor significantly affected the prognosis of the patients ($P = .0001$). The prognosis of AC was significantly better than the prognosis of both LCNEC and SCLC ($P = .0406$), which means that intermediate-grade malignancy (AC) could be differentiated from high-grade malignancy (LCNEC and SCLC). The survival curves of LCNEC and SCLC were superimposed, and there was no difference in survival ($P = .9147$). Survival was further analyzed within the same stage category, and a range of prognoses was seen. The relative grade of malignancy was reproduced within each stage category; in stage I patients (n = 175), the 5-year survival rates for TC, AC, LCNEC, and SCLC were 98.0%, 75.0%, 57.8%, and 42.2%, respectively (Fig 2). Again, there was no survival difference between LCNEC and SCLC ($P = .1851$), although the 5-year survival rate was numerically better for LCNEC. In stage II patients (n = 46), the 5-year survival rates for TC, AC, LCNEC, and SCLC were 75.0%, 100%, 31.9%, and 38.9%, respectively. In the multivariate analyses, the following variables were entered based on the results of univariate analyses: histologic type, symptoms, completeness of resection, nodal status, pathologic stage, and age. Among these variables, a histologic type of high-grade NE tumor was the most significant prognostic factor, with risk ratios (RRs) for SCLC and LCNEC of 17.40 and 17.69, respectively. Other significant prognostic factors included incomplete resection (RR = 3.13), symptoms (RR = 1.69), nodal involvement (RR = 2.23), and old age (RR = 1.53).

Table 3. Details of Histologic Diagnosis of SCLC

Histologic Type	No. of Patients	%
SCLC, not combined	83	73.4
SCLC, combined	30	26.6
With LCNEC	15	13.3
With AD	9	8.0
With SQ	5	4.4
With AD + SQ	1	0.9
Total	113	100

Abbreviations: LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma; AD, adenocarcinoma; SQ, squamous-cell carcinoma.

Table 4. Clinicopathologic Profiles According to the Histologic Type

Profile	Histologic Type TC (n = 55)	AC (n = 9)	LCNEC (n = 141)	SCLC (n = 113)	Total (N = 318)
Age, years					
Median	52	63	66	67	65
Range	17-83	38-73	38-88	40-84	17-88
Sex					
Female, No.	23	5	15	23	66
Male					
No.	32	4	126	90	252
%	58.2	44.4	89.4	79.7	79.3
Paraneoplastic syndrome					
No.	1	0	0	3	4
%	1.8	0	0	2.7	1.3
Present and past smokers					
No.	30	5	139	106	280
%	54.6	55.6	98.6	93.8	88.1

Abbreviations: TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma.

DISCUSSION

A population of NE cells can be recognized in the normal bronchoalveolar structures in the lung, where NE defines specific cellular characteristics and the ability to uptake and decarboxylate amine precursors.[1] These features are reflected by the morphology, such as

Table 5. Percentage of Abnormal Elevations of the Tumor Markers CEA, NSE, and proGRP

	Histologic Type											
	TC (n = 55)			AC (n = 9)			LCNEC (n = 141)			SCLC (n = 113)		
Tumor Marker	%	No. of Patients With Abnormally Elevated Serum Level	No. of Patients Measured	%	No. of Patients With Abnormally Elevated Serum Level	No. of Patients Measured	%	No. of Patients With Abnormally Elevated Serum Level	No. of Patients Measured	%	No. of Patients With Abnormally Elevated Serum Level	No. of Patients Measured
CEA	5.9	3	51	11.1	1	9	48.5	63	130	40.7	44	108
NSE	0	0	42	0	0	5	12.4	13	105	2.3	2	88
proGRP	7.1	1	14	100	1	1	25.8	8	29	48.5	16	31

Abbreviations: TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma; LCC, large-cell carcinoma; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; proGRP, progastrin-releasing peptide.

secretory granules and dense core granules by electron microscopy. However, the clinical implications of these NE characteristics (NE phenotype and NE morphology) in lung tumors have not yet been defined, especially in relation to the proper choice of treatment strategy. For SCLC, which shows a chemosensitive and aggressive nature, a standard therapeutic strategy has been established apart from other histologies. However, other NE tumors require the further refinement of histology-specific treatment.

NE lung tumors exhibit a spectrum of histologies, clinical profiles, and biologic behaviors ranging from relatively indolent TC to histologically high-grade, biologically aggressive tumors.[2-5] The grading was proposed in the 1999 WHO classification, with rigorous criteria for each subtype, even though LCNEC is still considered a variant form of large-cell carcinoma.[14] According to the WHO classification, AC can be differentiated from TC by a higher mitotic activity and/or the presence of necrosis. Although LCNEC is characterized by the NE morphology (nesting, palisading, and rosettes), a high mitotic rate, necrosis, cytologic features similar to non–small-cell lung cancer, and positive immunohistochemical staining for NE markers, it can sometimes be difficult to differentiate between LCNEC and SCLC. Even for an expert pathologist, the cytologic features falling between LCNEC and SCLC can make it difficult to define the histology as either SCLC or LCNEC, as seen in 14 tumors in the present series. One of the issues in the present WHO classification is that, despite the morphologic and clinical close relationship between SCLC and LCNEC, these tumors are placed in different categories. Specifically, LCNEC is recognized as a part of non–small-cell carcinoma, and the present therapeutic strategy is being planned in a histology-specific basis as SCLC or non-SCLC. Further assessment of therapeutic response is a high-priority issue, which will also justify the distinction between LCNEC and SCLC.

The most significant clinical and pathologic implication of the present study is the determination of the relative grade of malignancy of each histologic type among NE tumors. In particular, for the three

Table 6. Pathologic Profiles According to the Histologic Type

	Histologic Type									
	TC (n = 55)		AC (n = 9)		LCNEC* (n = 141)		SCLC (n = 113)		Total (N = 318)	
Profile	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Tumor diameter, mm										
Mean	26		26		41		29		34	
Range	9-70		13-44		7-140		7-75		7-140	
Postsurgical stage										
I	50	90.9	4	44.4	63	45.3	58	51.3	175	55.4
II	4	7.3	2	22.2	22	15.9	18	16.0	46	14.6
IIIA	1	1.8	2	22.2	32	23.0	24	21.2	59	18.7
IIIB	0	0	0	0	13	9.4	12	10.6	25	7.9
IV	0	0	1	11.1	9	6.5	1	0.9	11	3.5
Nodal involvement										
N0	53	96.4	5	55.6	76	55.1	65	57.5	199	63.2
N1	1	1.8	2	22.2	26	18.8	23	20.4	52	16.5
N2	1	1.8	2	22.2	33	23.9	24	21.2	60	19.1
N3	0	0.0	0	0.0	3	2.2	1	0.9	4	1.3

Abbreviations: TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma.
*Data on the stage and nodal status were not available in two and three patients with LCNEC, respectively.

Table 7. Outcome of Patients With NE Tumors

Outcome	Histologic Type: TC (n = 55) No. of Patients	%	AC (n = 9) No. of Patients	%	LCNEC (n = 141) No. of Patients	%	SCLC (n = 113) No. of Patients	%	Total (N = 318) No. of Patients	%
Tumor recurrence	2	3.6	3	33.3	68	48.2	54	47.8	124	39.0
Locoregional	1		1		17		10		30	
Distant	1		2		34		18		55	
Both	0		0		16		16		36	
Unknown	0		0		1		1		4	
All deaths	3	5.5	2	22.2	84	59.6	69	61.1	158	49.7
Cancer death	1	33.3	0	0.0	62	73.8	43	63.2	106	67.5

Abbreviations: TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; SCLC, small-cell lung carcinoma; NE, neuroendocrine.

histologic types that are considered intermediate- or high-grade malignancy (AC, LCNEC, and SCLC), the present findings clearly revealed their relative prognoses. There have been several previous reports on the prognosis of NE tumors of the lung. However, relatively few cases of high-grade NE tumors have been included. On the basis of their own diagnostic criteria, Travis et al[5] reported that the 5-year survival rates for TC, AC, LCNEC, and SCLC were 87%, 56%, 27%, and 9%, respectively. Garcia-Yuste et al[4] reported that the 5-year survival rates for TC, AC, LCNEC, and SCLC were 96%, 72%, 21%, and 14%, respectively. Neither report described a significant difference in survival between LCNEC and SCLC. As for LCNEC, the reported 5-year survival rates have ranged from 13% to 47%.[4,-6,9,11,12] The 5-year survival rate of LCNEC in our present series was 41.3%, which is within the range of the rates reported previously. Even for stage I disease, the reported 5-year survival rates have been approximately 10% to 30%.[4,6,9,12] In the present series, however, the 5-year survival rate of stage I LCNEC was 60%, which was higher than the rates in previous reports. However, considering the 5-year survival rate of stage I non–small-cell lung cancer, LCNEC is the histology with the worst prognosis among non–small-cell histologies.[15] Also, we confirmed that LCNEC shows almost the same prognosis as SCLC. These two histologies also shared similar clinicopathologic backgrounds, such as smoking history and sex.

In high-grade NE tumors, the existence of borderline cases between LCNEC and SCLC has been noted. In the process of central pathologic review of the present study, there were 14 borderline cases between LCNEC and SCLC, which required another session of panel meetings to reach the consensus regarding the histology as either LCNEC or SCLC. There might be three factors that are closely related to the difficulties in the diagnosis; these are technical issues in the preparation of specimens, diagnostic reproducibility issues, and diagnostic criteria issues. There are several technical issues that make the diagnosis difficult. One is the poor histology as a result of poor fixation, extensive tumor necrosis, and sections that are cut too thick or poorly staining, although the preparation of the slides was completely centralized in the present study to minimize these issues. The histologic heterogeneity with the different cellular sizes and different proportions also affects the diagnosis.[16] The fact that the cell size in SCLC tends to be larger in the large, well-fixed specimens should be well recognized.[17]

It has been well known for SCLC that expert lung cancer pathologists disagree about the diagnosis in approximately 5% to 6% of the

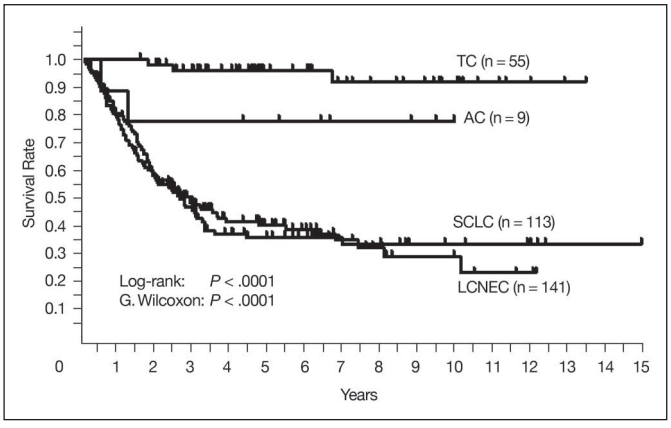

Fig 1. Overall survival curves in neuroendocrine tumors of all stages (N = 318) according to the following histologic types: TC, typical carcinoid (n = 55); AC, atypical carcinoid (n = 9); LCNEC, large-cell neuroendocrine carcinoma (n = 141); and SCLC, small-cell lung carcinoma (n = 113). The histologic type significantly affected the survival ($P < .0001$, log-rank test).

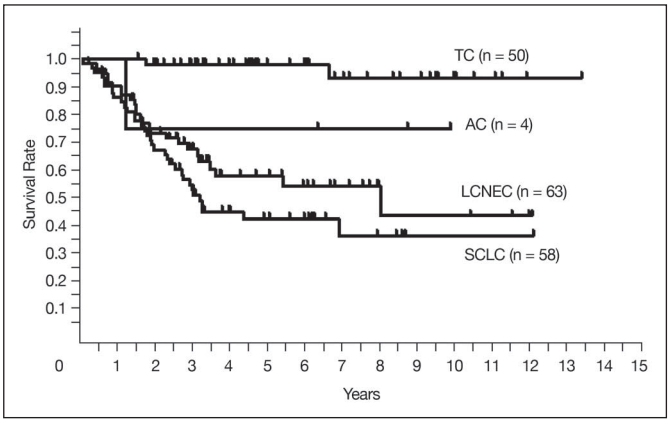

Fig 2. Overall survival curves in stage I neuroendocrine tumors (n = 175) according to the following histologic types: TC, typical carcinoid (n = 50); AC, atypical carcinoid (n = 4); LCNEC, large-cell neuroendocrine carcinoma (n = 63); and SCLC, small-cell lung carcinoma (n = 58). The histologic type significantly affected the survival ($P < .0001$, log-rank test).

cases.[18] In the present study, there was difficulty in the diagnosis of 14 tumors, which composed 5.5% of the 254 high-grade NE tumors; this percentage is quite similar to those previously reported. As part of the diagnostic criteria, the cellular and nuclear size is an important part in the differentiation between LCNEC and SCLC. According to the morphometric analysis by Marchevsky et al,[19] a considerable overlap of nuclear size was shown between LCNEC and SCLC, and the authors addressed that these two histologies should be merged as a single group of high-grade NE carcinoma. However, it is not clear how they could reach the definitive diagnosis as LCNEC or SCLC despite the overlapping cellular and nuclear size. These data, as well as our own, demonstrate that the cell size alone is insufficient as a criterion for establishing the diagnosis of high-grade NE tumors, and a constellation of criteria needs to be used. We still need more pathobiologic characteristics (and perhaps, they are more likely to be molecular rather than morphologic) to make the differentiation between SCLC and LCNEC clearer.

The limitations of this study must also be addressed. In this study, only surgical cases were collected to ensure that a thorough investigation of histopathologic features would be possible, and advanced, unresectable tumors were excluded. As is well known, most patients with SCLC are not candidates for resection because of local/systemic spread of the tumor. It is speculated that typical SCLC arises in the hilum and metastasizes to remote organs at a relatively early stage of the disease. In this sense, the resected SCLC in the present series may not represent typical SCLC, which might have a more aggressive nature. Although it will still be difficult to obtain enough specimens or to perform an immunohistochemical study using only biopsy samples in nonsurgical patients, future studies should include advanced diseases.

In conclusion, the present, large-scale, multi-institutional study defined the prognostic spectrum of pulmonary NE tumors as TC, AC, LCNEC, and SCLC, where LCNEC and SCLC were similarly aggressive. Future studies should clarify the histology-specific sensitivity to treatment, especially with regard to chemoradiotherapy. If similar responses are found, the histologic distinction at least has little significance in the planning of treatment strategy.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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