Problems in Diagnosis and Surgical Management of Clinical N1 Non-small Cell Lung Cancer

Shun-ichi Watanabe, MD, Hisao Asamura, MD, Kenji Suzuki, MD, and Ryosuke Tsuchiya, MD

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan

Background. Clinical diagnosis of the nodal status is a significant factor in determining the treatment and predicting the prognosis in lung cancer patients. A patient with clinical N1 (cN1) disease is usually considered to be a candidate for surgical intervention in the present staging system in non-small cell lung cancer (NSCLC). However, cN1 disease is a subset for which the method of treatment and surgical results are variable, simply because both upstaging and downstaging can occur. We evaluated the surgical and pathologic results of cN1 NSCLC patients to reveal the problems in diagnosis and surgical management for this subset.

Methods. From January 1998 to March 2003, 1,606 patients underwent thoracotomy for primary lung cancer at the National Cancer Center Hospital. Among them, the subjects for this study were 168 (10.5%) NSCLC patients who were clinically diagnosed as having N1 disease and underwent surgery without induction therapy.

Results. The tumor cell types of these 168 cN1 NSCLC patients were adenocarcinoma in 73 (44%) and squamous cell carcinoma in 79 (47%). Pneumonectomy was performed in 26% (n = 43) patients, bilobectomy in 15% (n = 25), and exploratory thoracotomy in 11% (n = 19). Of 19 exploratory thoracotomy cases, 10 cases were due to pleural dissemination. The pathologic nodal status of the 135 patients who underwent pulmonary resection and mediastinal dissection was pN0, 19% (n = 25); pN1, 44% (n = 59); and pN2–3, 37% (n = 51). Of the 55 adenocarcinomas, 60% (n = 33) were revealed to be N2 disease on pathologic examination. There were no significant differences in the serum tumor markers between the pN1 and pN2 groups. Among the 25 patients who were downstaged postoperatively (cN1-pN0), 21 patients (84%) showed obstructive pneumonia in the lung.

Conclusions. In the staging process of cN1 disease, it will be helpful to perform mediastinoscopy and thoracoscopy to avoid unnecessary thoracotomy especially in adenocarcinoma, even though mediastinal nodes and pleural dissemination were negative on computed tomography investigation. Since extensive pulmonary resection (bilobectomy or pneumonectomy) was required in 41% of the patients, preoperative detailed cardiopulmonary function tests should be mandatory to reduce surgical morbidity and mortality. On the other hand, when pneumonia due to airway obstruction by the tumor exists, false-positive hilar nodes can be expected.

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In the TNM classification of lung cancer, the preoperative evaluation of tumor (T) status is becoming more precise with the development of computed tomography (CT), whereas that of nodal (N) status continues to be unsatisfactory. Clinical diagnosis of N status is a significant factor in determining the method of treatment and predicting the prognosis in non-small cell lung cancer (NSCLC) patients. However, unexpected extensive nodal involvement is occasionally detected in the resected specimen, because the evaluation of clinical N (cN) status is based on the size of lymph nodes on CT. In contrast, tumor involvement sometimes can not be detected in swelling lymph nodes on pathologic examination when the patient had developed pneumonia due to airway obstruction by the tumor. Although most patients with cN1 disease are considered surgical candidates using the present TNM staging system, surgical results in cN1 disease can be variable, simply because both underestimation and overestimation of the N status can occur in this subset. To reveal the problems in diagnosis and surgical management for patients with cN1 disease, we retrospectively evaluated surgical and pathologic results of this subset.

Patients and Methods

From January 1998 to March 2003, 1,606 patients underwent thoracotomy for primary lung cancer at the National Cancer Center Hospital. Among them, the subjects for this study were 168 (10.5%) NSCLC patients who were clinically diagnosed as having N1 disease and underwent thoracotomy without induction therapy. Of these, 33 patients were excluded from pathologic nodal evaluation, consisting of 19 patients who underwent only exploratory thoracotomy, and 14 patients who did not undergo mediastinal nodal dissection because of unfavorable risks.

Basically, only CT was employed to determine clinical N status. Our criterion for lymph node enlargement is

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Address reprint requests to Dr Watanabe, Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan; e-mail: syuwatan@ncc.go.jp.

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Table 1. Patient Characteristics in Clinical N1 Nonsmall Cell Lung Cancer Patients

Characteristic	Number
Number of patients	168
Age (years)	
Range	26–81
Mean	62.5 ± 9.5
Sex	
Male	138 (82%)
Female	30 (18%)
Histological type	
Adenocarcinoma	73 (43%)
Squamous cell carcinoma	79 (47%)
Other	16 (10%)
Clinical T stage	
T1	27 (16%)
T2	90 (54%)
T3	38 (23%)
T4	13 (8%)
Size of primary tumor (cm)	
Range	1.3–15.0
Mean	5.2 ± 2.3

greater than 1.0 cm in the short axis of each nodal station on CT. Mediastinoscopy or positron emission tomography scan was not routinely employed preoperatively. Pathologic confirmation of lung cancer was not made if the nodule is highly suspected as lung cancer on CT scan.

Tumors were removed through posterolateral thoracotomy. A Naruke map in the classification of lung cancer issued by the Japan Lung Cancer Society was used for the designation of dissected nodal stations.

The serum carcinoembryonic antigen (CEA) level was measured in adenocarcinoma patients, and cytokeratine fragment (CYFRA) or squamous cell carcinoma antigen (SCC), or both, were measured in squamous cell carcinoma by enzyme immunoassay. The cut-off value was 5 ng/mL for CEA, 2.2 ng/mL for CYFRA, and 1.5 ng/mL for SCC.

Mean values are expressed as mean ± standard deviation throughout the article. The χ^2 test was used for statistical analyses, and a value of p less than 0.05 was considered to be significant.

Results

Patient Characteristics

The patient characteristics of the 168 patients are shown in Table 1. The patients consisted of 138 men and 30 women with a mean age of 62.5 years (range, 26 to 81). The tumor cell types of these 168 cN1 NSCLC patients were adenocarcinoma in 73 (43%), squamous cell carcinoma in 79 (47%), and other cell types in 16 (10%).

Table 2. Surgical Procedures in Clinical N1 Nonsmall Cell Lung Cancer Patients

Surgical Procedure	Number
Pneumonectomy	43
Bilobectomy	25
Lobectomy	80
With bronchoplasty	10
With vascular plasty	6
With bronchovascular plasty	3
Segmentectomy or less	1
Exploratory thoracotomy	19
Due to pleural dissemination	10
Due to aortic invasion	2
Due to vertebral invasion	1
Due to extensive nodal involvement	6

Preoperative evaluation of T status by CT was T1 in 27 cases, T2 in 90, T3 in 38, and T4 in 13. The mean tumor diameter was 5.2 ± 2.3 cm.

Surgical Procedure

Pneumonectomy was performed in 43 patients (26%), bilobectomy in 25 (15%), lobectomy in 80 (48%), segmentectomy in 1, and exploratory thoracotomy in 19 (11%). Among the 80 lobectomy patients, 19 (24%) underwent plasty of the bronchus or pulmonary artery, or both (Table 2). The reasons for the 19 exploratory thoracotomies were unresectable T4 disease in 13 patients (pleural dissemination in 10, aortic invasion in 2, and vertebral invasion in 1) and extensive nodal involvement in 6 (Table 2).

Tumor Cell Type and Nodal Status

The tumor cell type, clinical T status, and pathologic nodal status in the 135 patients who underwent pulmonary resection and mediastinal nodal dissection are shown in Table 3. The nodal status of these 135 cases was pN0, 25 (19%); pN1, 59 (44%); and pN2-3, 51 (37%). The incidence of pN2-3 was not influenced by T status (T1-2, 38%; T3-4, 37%). Sixty percent of all adenocarcinomas (33 of 55) and 68% of T1-2 adenocarcinomas (27 of 40) were revealed to be N2 on pathology examination. On the other hand, among 68 squamous cell carcinomas, 79% (n = 54) were pN0-1.

Serum Tumor Markers

Of 55 adenocarcinoma patients, 26 patients (47%) showed an abnormal level of CEA, and consisted of 3 N0 patients (41%), 7 N1 (44%), and 16 N2 (49%). Among the 68 squamous cell carcinoma patients, 43 patients (63%) showed an abnormal level of serum tumor marker (CYFRA or SCC), and consisted of 7 N0 patients (41%), 27 N1 (73%), and 9 N2 (64%). There were no significant differences in the serum tumor markers between the pN1 and pN2 groups in each cell type.

Table 3. Cell Types, Clinical T Status, and Pathological N Status in 135 Patients Who Underwent Pulmonary Resection and Mediastinal Dissection

Cell Type	Clinical T Status	No. of Patients	Pathological N Status		
			N0	N1	N2,3
Adenocarcinoma	All	55	6 (11%)	16 (29%)	33 (60%)
	T1, T2 (Stage 2)	40	3 (8%)	10 (25%)	27 (68%)
	T3, T4 (Stage 3)	15	3 (20%)	6 (40%)	6 (40%)
Squamous cell carcinoma	All	68	17 (25%)	37 (54%)	14 (21%)
	T1, T2 (Stage 2)	46	12 (26%)	26 (57%)	8 (17%)
	T3, T4 (Stage 3)	22	5 (23%)	11 (50%)	6 (27%)
Other	All	12	2 (17%)	6 (50%)	4 (33%)
	T1, T2 (Stage 2)	8	2 (25%)	5 (63%)	1 (13%)
	T3, T4 (Stage 3)	4	0	1 (25%)	3 (75%)
Total	All	135	25 (19%)	59 (44%)	51 (37%)
	T1, T2 (Stage 2)	94	17 (18%)	41 (44%)	36 (38%)
	T3, T4 (Stage 3)	41	8 (20%)	18 (44%)	15 (37%)

Incidence of Obstructive Pneumonia in Downstaged Cases

Table 4 shows the incidence of obstructive pneumonia in patients with false-positive N1 nodes (cN1-pN0). In total, 25 patients (19%) were downstaged postoperatively, and 23 of these 25 patients (84%) were histologically proven to have obstructive pneumonia in the resected lungs.

Comment

In the article by Mountain [1] on revision of the lung cancer staging system, only 5% had cN1 disease in surgical patients, showing cN1 disease is a minor entity in surgical candidates. Clinical diagnosis of the nodal status is a significant factor to decide the treatment and predict the prognosis in NSCLC patients. In the present staging system, most of the clinical N0 and N1 disease is basically considered to be a candidate for surgical resection unless the tumor is unresectable T4 disease, whereas N2 disease is to be a candidate for chemoradiotherapy. Therefore, cN1 disease is a borderline subset for which the treatment can go different ways, simply because both underestimation and overestimation of the nodal status can easily occur in this group of patients.

Computed tomography scan has been used for the clinical diagnosis of nodal status in the staging system. In spite of the development of the helical CT scanner, the preoperative evaluation of intrathoracic nodal status by CT scan remains difficult, mainly because many cancer-positive nodes of normal size exist, especially in adenocarcinoma cases [2–5]. The overall sensitivities of CT scan for N factor is reportedly about 64% to 79% [6, 7]. About 20% of false-negative nodes on CT scan have been reported, even in small-sized adenocarcinoma cases [8, 9]. As shown in Table 3, 60% of all cN1 adenocarcinoma and 68% of cT1-2N1 adenocarcinoma patients were histologically revealed to be N2 after thoracotomy in our series. Preoperative evaluation of nodal status by CT scan is thus not accurate enough to establish the appropriate therapeutic strategy [5, 6]. Furthermore, 11.3% of cN1 patients (19 of 168) in our series underwent only exploratory thoracotomy because of unresectable T4 disease (n = 13) or extensive nodal involvement (n = 6) as shown in Table 2. Among the 13 cases of unresectable T4 disease, 10 (77%) were due to pleural dissemination. Preoperative evaluation of T status is also revealed to be unsatisfactory, especially for pleural dissemination. Although the clinical N1 NSCLC patient is a candidate for surgical resection in the present staging system, it would be helpful to perform mediastinoscopy and thoracoscopy for cN1 disease to avoid unnecessary thoracotomy, even though mediastinal nodes or pleural dissemination were negative on CT investigation [10].

Table 4. The Incidence of Obstructive Pneumonia in Downstaged (cN1–pN0) Patients

Cell Type	No. of cN1–pN0 Patients	Patients Showing Obstructive Pneumonia	
		No.	%
Adenocarcinoma (n = 55)	6 (11%)	4	67
Squamous cell carcinoma (n = 68)	17 (25%)	15	88
Other (n = 12)	2 (17%)	2	100
Total (n = 135)	25 (19%)	21	84

Riquet and associates [11] reported that lung cancer easily metastasizes to the mediastinum. Keller and associates (Eastern Cooperative Oncology Group) [12] reported that complete mediastinal lymph node dissection had identified significantly more levels of mediastinal involvement than systematic sampling. Systematic nodal dissection will be indispensable in adenocarcinoma patients for accurate intrathoracic staging [13].

In contrast with the above, the existence of obstructive pneumonia sometimes caused overestimation of nodal involvement, that is, a false-positive node, as shown in Table 4. Takamochi and coworkers [14] reported that

smoking history, presence of obstructive pneumonia, or other factors were significant factors of false-positive scans in mediastinal nodes on CT. Also regarding the hilar nodes, we consider that false-positive nodes can be expected if the obstructive pneumonia exists within the lung.

Regarding the preoperative serum tumor marker investigation, we failed to show the usefulness of serum tumor marker measurement for discrimination of N1 and N2 disease in all cell types. Carcinoembryonic antigen is an antibody extracted from colon cancer [15], and has been used as a specific tumor marker for digestive cancers and lung cancer [16, 17]. In this study, 49% of pN2 and 44% of pN1 adenocarcinoma patients showed elevated serum CEA levels, with no significant differences. These incidences are similar to that of stage IIIA patients with mediastinal involvement reported by Vincent and coworkers [16]. The combination of SCC and CYFRA also revealed not to be useful tumor marker for discrimination of N1 and N2 disease in squamous cell carcinoma.

The type of resection can also be variable in this subset, such as lobectomy, bilobectomy, or pneumonectomy, depending on intraoperative findings of nodal status. We do not perform pneumonectomy when the N1 node is mobile. In our series of resected cases, 41% of patients (68 of 135) underwent extensive resection of lung parenchyma (pneumonectomy, 26%; and bilobectomy, 15%), despite of our aggressive attitude to perform the plasty of the bronchus or pulmonary artery as shown in Table 2. In view of perioperative cardiopulmonary management, preoperative meticulous evaluation of pulmonary and cardiac function test will be mandatory for cN1 disease [18].

Collectively, in staging process of cN1 disease, meticulous evaluation of N and T status using mediastinoscopy and thoracoscopy will be necessary to avoid unnecessary thoracotomy. Because bilobectomy or more resection is often required, preoperative detailed cardiopulmonary function tests will be mandatory to reduce the morbidity and mortality. On the other hand, when the obstructive pneumonia exists within the lung, false-positive nodes can be expected.

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Institutional report - Thoracic general

The new strategy of selective nodal dissection for lung cancer based on segment-specific patterns of nodal spread☆

Shun-ichi Watanabe*, Hisao Asamura, Kenji Suzuki, Ryosuke Tsuchiya

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan

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Abstract

A new strategy for selective nodal dissection in non-small cell lung cancer (NSCLC) patients according to the segment of primary tumor was explored. Data on 504 patients with NSCLC of less than 5 cm, histologically revealed to be N2 disease after thoracotomy, were analyzed. In right upper lobe (RUL) tumor, when the pretracheal node was negative, the incidence of subcarinal involvement was 3.8%. In lower lobe tumor, superior segment (RLL-Superior and LLL-Superior) tumor showed a significantly higher incidence of superior mediastinal involvement than basal segment (RLL-Basal and LLL-Basal) tumor (right, $P=0.0036$; left, $P=0.0499$). When the subcarinal node was negative, the incidence of superior mediastinal metastasis in RLL-basal and LLL-Basal tumor was 11% and 8%, respectively. In left upper lobe tumor, superior segment (LUL-Superior) tumor showed a significantly lower incidence of subcarinal involvement than lingular segment (LUL-Lingular) tumor ($P=0.0381$). When aortic nodes were negative in LUL-Superior tumor, the incidence of subcarinal metastasis was 6%. Collectively, in RUL and LUL-Superior tumors, subcarinal dissection may be unnecessary if superior mediastinal node is negative. In RLL-Superior and LLL-Superior tumors, extensive dissection is required. In RLL-Basal and LLL-Basal tumors, superior mediastinal dissection may be unnecessary if subcarinal node is negative.

Keywords: Selective nodal dissection; N2; Systematic nodal dissection; Non-small cell lung cancer

1. Introduction

Since Cahan (1960) [1] reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called radical lobectomy, this procedure has been a standard surgery for lung cancer. In 1978, Naruke [2] suggested an anatomical map in which the lymph node stations were numbered, and since then this map has been used for nodal dissection. With this map, extensive nodal dissection including the superior and inferior mediastinum has been universally performed in lung cancer surgery. This technique, termed systematic nodal dissection (SND) remains an important component of the investigative and therapeutic process in all patients undergoing thoracotomy for lung cancer.

However, as the number of early-detected lung cancers is increasing with the recent development of the CT scanner, the extent of nodal dissection for lung cancer should be tailored to each case. That is, more selective dissection should be undertaken especially for early cancer by considering the tumor location-specific lymphatic pathway, simply because nodal involvement is not so extensive in many cases. In this study, a new strategy for selective nodal dissection in non-small cell lung cancer (NSCLC) patients based on segment-specific patterns of nodal spread was explored.

2. Materials and methods

2.1. Patients

Data on 504 patients with NSCLC less than 5 cm, histologically revealed to be N2 disease between January 1977 and October 2003, were analyzed. Tumors invading the other lobe were excluded. All patients underwent at least lobectomy with hilar and mediastinal lymphadenectomy. The correlation between the segment of the tumor location and the involved hilar/mediastinal nodes were investigated in each case.

2.2. Surgical procedure

Pulmonary resection and SND were performed through posterolateral thoracotomy. At thoracotomy the diagnosis was confirmed by frozen-section analysis, if histological confirmation was not available preoperatively. Systematic nodal dissection, including the superior to inferior mediastinum, was then performed after pulmonary resection. In left thoracotomy, upper mediastinal dissection indicated aortic (#5, 6) and tracheobronchial (#4) node dissection.

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*Corresponding author: Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan.
Fax: +81-3-3542-3815.
E-mail address: syuwatan@ncc.go.jp (S. Watanabe).

Table 1
Patient characteristics in pathological N2 non-small cell lung cancer patients less than 5 cm in size

Number of patients	504
Histological type	
Adenocarcinoma	367 (72.8%)
Squamous cell carcinoma	99 (19.6%)
Large cell carcinoma	27 (5.4%)
Adenosquamous carcinoma	9 (1.8%)
Others	2 (0.4%)
Tumor location	
Right	303
upper lobe	183
middle lobe	25
lower lobe	95
Left	201
upper lobe	140
lower lobe	61

2.3. Patient characteristics

Patient characteristics are shown in Table 1. The tumor cell types were adenocarcinoma in 367 (72.8%), squamous cell carcinoma in 99 (19.6%), large cell carcinoma in 27 (5.4%) and adenosquamous cell carcinoma in 9 (1.8%). Right thoracotomy was performed in 303 patients and left in 201. The lobe of origin was the right upper lobe (RUL) in 183 patients, right middle lobe (RML) in 25, right lower lobe (RLL) in 95 in 41 of whom it was the superior segment, left upper lobe (LUL) in 140 in 122 of whom it was the superior segment, and left lower lobe (LLL) in 61 in 23 of whom it was the superior segment.

2.4. Statistical analysis

The statistical significance of differences was determined using the chi-square test for independence. Relative risk and 95% confidence intervals were calculated. Values of P less than 0.05 were considered to be statistically significant.

3. Results

3.1. RUL tumor

The incidence of subcarinal involvement in RUL tumor was 18% (33/183). However, when the pretracheal lymph node (#3) was negative, the incidence was only 3.8% (7/183). There were no significant differences in patterns of lymphatic pathway between the apical, posterior and anterior segments within the RUL.

Table 2
The incidence of upper mediastinal metastasis in superior and basal segment tumor of the lower lobe

Side	Location of the primary tumor	No. of patients	Metastasis to the superior mediastinal nodes		
			No.	%	P value
Right	Superior segment	41	26	63	0.0036
	Basal segment	54	18	33*	
Left	Superior segment	23	15	65	0.0499
	Basal segment	38	15	39**	

* When subcarinal lymph node (#7) was negative, the incidence of superior mediastinal (#1–4) metastasis was 9% (5/54).
** When subcarinal lymph node (#7) was negative, the incidence of superior mediastinal (#4, 5, 6) metastasis was 8% (3/38).

3.2. RML tumor

The incidence of superior mediastinal (#1–4) and subcarinal (#7) involvement was 52% (13/25) and 72% (16/25), respectively. The incidence of lower mediastinal involvement was 8% (2/25). There were no significant differences in patterns of lymphatic pathway between lateral and medial segment within the RML.

3.3. RLL and LLL tumor

Among all of the segments in the lower lobe, 5 segments in the right lung and 4 in the left, there were significant differences in patterns of lymphatic pathway between the superior and basal segments on both sides, as shown in Table 2. The incidence of superior mediastinal involvement in superior segment tumor (right 65%, 26/41; left 65%, 15/23) was higher than that in basal segment tumor (right 33%, 18/54; left 39%, 15/38), with significant differences (right, $P=0.0036$; left, $P=0.0499$). When the subcarinal lymph node (#7) was negative, the incidence of superior mediastinal metastasis in RLL-basal and LLL-Basal segment tumor was 9% (5/54) and 8% (3/38), respectively.

3.4. LUL tumor

There were significant differences in patterns of lymphatic pathway between the superior and lingular segments within the LUL, as shown in Table 3. Superior segment tumor showed a significantly lower incidence of subcarinal involvement (14%, 17/122) than lingular segment tumor (33%, 6/18) ($P=0.0381$). When aortic lymph nodes (#5, 6) were negative in superior segment tumor, the incidence of subcarinal metastasis was 6% (7/122).

Collectively, the following eight segments, four in each side lung, with specific lymphatic pathways were identified: RUL ($n=183$), RML ($n=25$), superior segment of the RLL (RLL-Superior, $n=41$), basal segment of the RLL (RLL-Basal, $n=54$), superior segment of the LUL (LUL-Superior, $n=122$), lingular segment of the LUL (LUL-Lingular, $n=18$), superior segment of the LLL (LLL-Superior, $n=23$) and basal segment of the LLL (LLL-Basal, $n=38$). Based on the abovementioned patterns of nodal spread, the proper strategy for the selective lymph node dissection of each segment is shown in Table 4.

4. Discussion

The pathological nodal status in lung cancer patients is not always the same as that predicted by pre-operative investigations. For TNM classification, CT scan has been used in the clinical diagnosis of nodal status, however, the sensitivity of CT scan for the N factor is reported about 64 to 77% [3]. Since a high incidence of false-negative nodes on CT scan has been reported [4], systematic nodal dissection (SND), which means extensive mediastinal dissection including superior to inferior mediastinum, has been per-

Table 3
The incidence of superior mediastinal and subcarinal metastasis in superior and lingular segment tumor of the left upper lobe

Location of the primary tumor in the left upper lobe	No. of patients	Metastasis to the superior mediastinal nodes (#4,5,6)			Metastasis to the subcarinal node (#7)		
		No.	%	*P* value	No.	%	*P* value
Superior segment	122	118	97	NS	17	14*	0.0381
Lingular segment	18	13	72		6	33	

* When aortic nodes (#5, 6) were negative, the incidence of subcarinal metastasis was 6% (7/122).

formed for lung cancer patients undergoing thoracotomy. Pathological evaluation of nodal involvement at the mediastinal and hilar levels is essential for detailed assessment of the disease extent.

Graham and associates [5] suggested that SND could disclose unexpected N2 disease, irrespective of cell type, the size, location and lobe of origin of the primary tumor, and whether prior mediastinoscopy had been performed. Keller and associates [6] suggested that cure rates could be improved by SND. Therefore, SND has been accepted as an important component of the investigative and therapeutic process in NSCLC patients.

With the development of the CT scanner and the increased incidence of lung cancer, the number of early-stage lung cancer is rising. The incidence of small-sized lung cancer among resected primary lung cancers in recent years has exceeded 20% in Japan [4,7]. As the number of early-detected lung cancers is increasing, a new therapeutic strategy for nodal dissection is required. Proposals of limited surgery for lung cancer have been undertaken in some previous reports [8–10].

There are two methods of limited surgery, one is lung parenchyma-preserving surgery and the other is limited nodal dissection. Regarding the lung parenchyma-preserving surgery, Lung Cancer Study Group (LCSG) [11] reported the results of a randomized trial of lobectomy versus limited resection for T1N0 NSCLC. They observed a 75% increase in recurrence and a 50% increase in cancer death in the patients undergoing segmentectomy or wedge resection, compared to those in the patients who underwent lobectomy. It is difficult to select candidate patients for limited resection, because cT1N0 lung cancer patients show nodal disease with a 15 to 25% incidence [4,7].

As for limited lymph node dissection, Riquet and associates [12] reported that lung cancer metastasizes so easily to the mediastinum that selection of the patients for limited surgery should be discussed carefully. Some previous reports have described the appropriateness of selective nodal dissection based on the lobe-specific extent of nodal spread [13–15]. In this study, we evaluated more meticulous data of the lymphatic pathway in not only T1 but also T2 tumors, to collect as much data as possible, and proposed a method of limited dissection from these results as shown in Table 4. The strategy of lymph node dissection should be changed from extensive dissection to selective dissection especially in early stage cancer or poor risk patients, because selective dissection will be able to reduce postoperative morbidity, such as bronchopleural fistula, chylothorax or recurrent nerve palsy. The establishment of a universally accepted method of selective nodal dissection for lung cancer would be indispensable.

5. Conclusions

Based on the patterns of nodal spread, a proper strategy for selective lymph node dissection of each segment was proposed as shown in Table 4. In RUL and LUL-Superior tumors, subcarinal dissection may be unnecessary if the superior mediastinal node is negative on frozen section. In RML and LUL-Lingular tumors, superior mediastinal and subcarinal dissection is necessary. In RLL-Superior and LLL-Superior tumors, extensive systematic dissection is routinely required. In RLL-Basal and LLL-Basal tumors, superior mediastinal dissection may be unnecessary if the subcarinal node is negative on frozen section.

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Table 4
The strategy of selective nodal dissection based on segment-specific patterns of nodal spread

	Location of the main tumor			
	RUL LUL-Superior	RML LUL-Lingular	RLL-Superior LLL-Superior	RLL-Basal LLL-Basal
Superior mediastinal nodes *3	⊙	⊙	⊙	○*2
Inferior mediastinal nodes				
Subcarinal node (#7)	○*1	⊙	⊙	⊙
Paraesophageal (#8) and pulmonary ligament (#9) nodes	×	×	⊙	⊙

⊙ dissection is advisable, ○ dissection is not always necessary, × dissection will be unnecessary.
*1: dissection may be unnecessary if pretracheal node (#3) is negative on frozen section.
*2: dissection may be unnecessary if subcarinal node (#7) is negative on frozen section.
*3: #1–4 for the right side, and #4–6 for the left.

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Appendix. Conference discussion

Dr. P. van Schil *(Edegem, Belgium)*: I think this is especially important as within the ESTS we are working on guidelines for peroperative mediastinal staging.

I have two questions for you. Did you observe any difference with the previous studies performed by Japanaese surgeons; for example, the classical studies by Naruke? Secondly, you state that you do segment-specific nodal dissection. On the other hand, you consider the upper lobe and the middle lobe just as 1 segment, but, in fact, anatomically there are 3 segments in the upper lobe and 2 in the middle lobe, or doesn't it matter for those 2 lobes?

Dr. Watanabe: Let me anaswer the second question first. I checked all of the segments in the right upper lobe and middle lobe, that is, the apical, posterior and anterior segment in the upper lobe, and the lateral and medial segment in the middle lobe. But there are no specific pathways among those segments, so I divided just the right upper lobe and the right middle lobe.

I'm sorry, what was the first question?

Dr. van Schil: Did you observe any differences with previous studies performed by the Japanese surgeos; for example, the studies by Naruke?

Dr. Watanabe: Unfortunately, no.

Dr. D. Branscheid *(Grosshandsdorff, Germany)*: Do you think that there are sometimes reasons why the lymph nodes are flowing more in a certain direction and all of a sudden there are 2 or 3 and the flow is to another side? Did you check if they have had tuberculosis or other infections? Have those lymph nodes been enlarged or have they been normal on the CR scan? Can you give us something about that?

Dr. Watanabe: I didn't check all of your suggestions. We basicaly do surgery only for clinical N0 and N1 patients.

Dr. Branscheid: Let me just ask another question. When the situation is like that, isn't it just an argument to do a complete dissectin and not say, okay, this node is not involved, therefore I probably do not need to take the next one? This is the consequence that I take out of your presentation. Is that wrong, or do you see it like that also a little bit?

Dr. Watanabe: Your question is why we are exploring the selective nodal dissection, why we don't do systematic nodal dissection?

Dr. Branscheid: No. Is the consequence to do a complete dissection? Is this your consequence out of that?

Dr. Watanabe: No. Recently, with the development of the CT scanner in Japan, we are getting a large number of early lung cancers. Basically we need to do systematic nodal dissection for lung cancer patients, but for early stage lung cancer we don't think systematic dissection is required for all of the tumors. This is the reason why we started this study. But the candidate in this study was the patients who underwent systematic dissection. So basically we think that systematic dissection is very important for lung cancer.

Dr. S. Elia *(Rome, Italy)*: You said that in 8 of 12 cases, actually in 66%, you would advice lymph node dissection. So you leave only 33% of lymph nodes that are actually doubtful. Would you feel safe in not performing complete lymphadenectomy in these patients? What is your conclusion?

Dr. Watanabe: I just took only pathological N2 patients. But among all patients, I mean N0, N1 and N2, if we included those patients, the incidence is going down, and I think the incidence will be one-third of this figure. So I think if the incidence is less thatn 10%, the incidence among all the lung cancer patients will be a few percent.

Dr. A. Turna *(Istanbul, Turkey)*: Could you tell us how many of your patients had mediastinoscopy before resection? Did you perform mediastinoscopy in these patients?

Dr. Watanabe: Very few: Basically we do mediastinoscopy for clinical N2 patients, and they are actually N2 on the mediastinoscopy. So we excluded those patients. In this study, the number of patients who underwent mediastinoscopy is very few.

Dr. B. Passlick *(Freiburg, Germany)*: What is your strategy for the future? Will you leave the upper mediastinal nodes in place if you have a right lower lobe tumor and a negative forzen section on the No. 7 lymph nodes?

Dr. Watanabe: We are now studying that kind of selective dissection. If the hilar lymph node and the No. 7 lymph node are negative in basal segment tumor, we can omit the upper mediastinal dissection. But now we are conducting only for poor-risk patients or very early lung cancer patients.

Radiologic Classification of Small Adenocarcinoma of the Lung: Radiologic-Pathologic Correlation and Its Prognostic Impact

Kenji Suzuki, MD, Masahiko Kusumoto, MD, Shun-ichi Watanabe, MD, Ryosuke Tsuchiya, MD, and Hisao Asamura, MD

Thoracic Surgery Division and Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan

Background. A new radiologic classification for small adenocarcinoma is necessary for discussions of limited surgical resection for peripheral lung cancer.

Methods. Between 1999 and 2003, 1,697 consecutive patients underwent pulmonary resection for lung cancer. Three hundred forty-nine of these patients with clinical stage IA lung cancer who had lung peripheral adenocarcinoma, 2 cm or less in size, were investigated retrospectively. Radiologic classification was based on the findings of thin-section computed tomographic scan such as the presence of solid and ground-glass opacity (GGO). Type 1 (n = 22), type 2 (n = 26), type 3 (n = 25), and type 4 (n = 43) show a simple GGO, an intermediate homogeneous increase in density, a halo, and a mixed area of GGO and a solid, respectively. Type 5 (n = 54) shows a solid tumor with GGO, and type 6 (n = 179) shows a solid tumor.

Results. There was no difference in the maximum tumor dimension among the six groups. All but 1 patient had no lymph node metastases among type 1 to 4 tumors, whereas these were found in 5% and 24% of the patients with type 5 and 6 tumors, respectively. Lymphatic invasions were rarely found in patients with type 1 to 4 tumors ($p < 0.001$).

Conclusions. Types 1, 2, 3, and 4 are considered to be radiologic early adenocarcinoma of the lung, and their pathologic features were minimally invasive. On the other hand, type 5 and 6 tumors could have lymph node metastases and are considered to be invasive adenocarcinoma. Although limited surgical resection may be enough for type 1 to 4 tumors, anatomic pulmonary resection should be recommended for type 5 or 6 tumor.

(Ann Thorac Surg 2006;81:413–20)

Several authors have reported that the incidence of adenocarcinoma of the lung has been increasing [1, 2]. The introduction of computed tomography (CT) for screening of lung cancer has made it possible to detect smaller pulmonary nodules. Most of those pulmonary nodules are peripherally located adenocarcinoma of the lung, and such early detection may be associated with attainment of cure through early intervention [3, 4]. Although there is a general consensus regarding the pathologic diagnosis of early adenocarcinoma of the lung [5–8], the clinical and radiologic diagnosis of early adenocarcinoma with favorable prognosis is still controversial. Several authors have reported that adenocarcinoma of the lung that shows a wide area of ground-glass opacity (GGO) has a good prognosis [4, 9–15]. However, there is no generally accepted method for measuring the area of GGO, as it is sometimes difficult to divide peripherally located adenocarcinomas according to the existing classification. Thus, a new classification of peripherally located adenocarcinoma of the lung is necessary, and in this study we sought to determine how to best classify peripherally located adenocarcinoma of the lung retrospectively.

Patients and Methods

Patient Characteristics

Between January 1999 and December 2003, 1,697 consecutive patients underwent pulmonary resection for lung cancer. Among them, 349 patients with clinical stage IA lung cancer who had peripherally located adenocarcinoma of the lung 2 cm or less in size were investigated in this study. Patients who received preoperative treatment, such as radiotherapy or chemotherapy, or who had multiple lung cancers were excluded from the study. Informed consent was obtained from the patients. Of these, 167 were men and 182 were women. Their ages ranged from 23 to 89 years, with a median of 64 years.

Radiologic Evaluation

Contrast-enhanced CT scan was performed using a TCT 900S or X-Vigor (Toshiba, Tokyo, Japan), and 10-mm-thick contiguous collimation was used to evaluate the entire lung for preoperative staging. The size of tumors was determined digitally based on the findings of thin-section CT

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Address correspondence to Dr Suzuki, Thoracic Surgery Division, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan; e-mail: kjsuzuki@ncc.go.jp.

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Table 1. Radiologic Classification of Small Adenocarcinoma of Lung by Means of Thoracic Thin-Section Computed Tomography

Class	Radiologic Findings
Type 1	Pure (simple) GGO
Type 2	Semiconsolidation (an area of intermediate homogeneous increase in density)
Type 3	Halo (area consisting of solid part and surrounding GGO halo)
Type 4	Mixed (an area consisting of GGO and solid part having air-bronchogram)
Type 5	Solid pattern with GGO[a]
Type 6	Solid pattern

[a] The area of GGO should be less than 50%.

GGO = ground-glass opacity.

scan. We perform thin-section cuts for every lung tumor 2.0 cm or less in maximal dimension. All tumors were subsequently evaluated with thin-section CT scan. Helical scans with 2-mm collimation were performed through a primary tumor. Images were reconstructed with a high-frequency algorithm, and photographed with a window level of −600 H and a window width of 2,000 H, as a "lung window." Radiologic findings were evaluated by two observers (M.K. and K.S.), who were not informed of the pathologic and prognostic outcome, on thin-section CT scan.

Radiologic Criteria for Grouping

The radiologic findings evaluated were as follows: the maximal tumor dimension, the presence and extent of solid or GGO component in tumor, and homogeneity of tumor. The solid (or consolidation) component was defined as an area of increased opacification more than 5 mm in diameter, which completely obscured underlying vascular markings. Ground-glass opacity was defined as an area of a slight, homogeneous increase in density, which did not obscure underlying vascular markings. Semiconsolidation was defined as an area of an intermediate homogeneous increase in density, which did not obscure underlying vascular markings. A halo was an area that consisted of a solid part and a surrounding GGO halo. Mixed was an area with a heterogeneous increase in density, which consisted of GGO and a solid part with an air-bronchogram. We divided the 373 small adenocarcinomas of the lung into six groups based on the extent of the solid component, presence of GGO, and homogeneity of the tumors (Table 1, Fig 1). Type 1 and 2 tumors are homogeneous in density, and lack a solid component (Figs 2, 3). The density of the tumor distinguishes type 1 from type 2. Type 3 and 4 tumors are heterogeneous in density, and the solid component comprises less than 50% of its diameter. The patterns of the solid component and GGO distinguish type 3 from type 4 (Figs 4, 5). Type 5 and 6 tumors are those that predominantly have a solid component. The presence of GGO distinguishes type 5 from type 6 (Figs 6, 7).

Clinicopathologic Factors and Statistical Consideration

The medical record of each patient was examined for age, sex, histologic tumor type, mode of surgery, serum carcinoembryonic antigen (continuous variable; nanograms per milliliter), pathologic nodal status, lymphatic invasion, vascular invasion, pleural invasion, and intrapulmonary metastasis. Skip metastasis was defined as any mediastinal lymph node involvement by lung cancer without N1 disease. The relationships between these pathologic factors and radiologic classification were investigated in this study to elucidate the prognostic significance of our radiologic classification of peripherally located adenocarcinoma of the lung. To compare two factors, Fisher's exact test was used for statistical analysis. Univariate and multivariate analyses were used to determine which clinical factors predict nodal involvement, such as N1 disease or skip metastasis. Univariate and multivariate analyses were performed by logistic regression analysis using StatView 5.0 (SAS Institute, Inc, Cary, NC). Forward and backward stepwise procedures

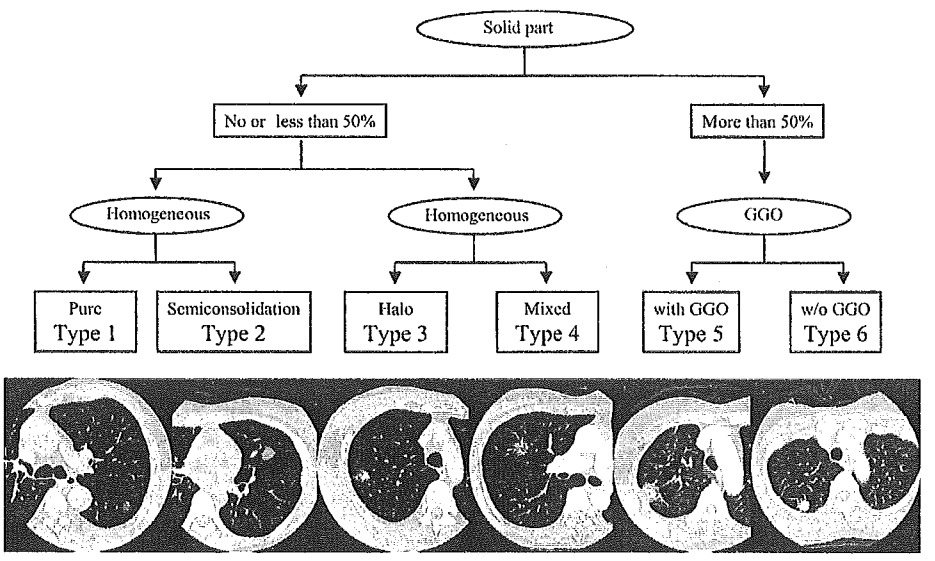

Fig 1. Flow chart for the new classification of small adenocarcinoma of the lung. (GGO = ground-glass opacity; w/o = without.)

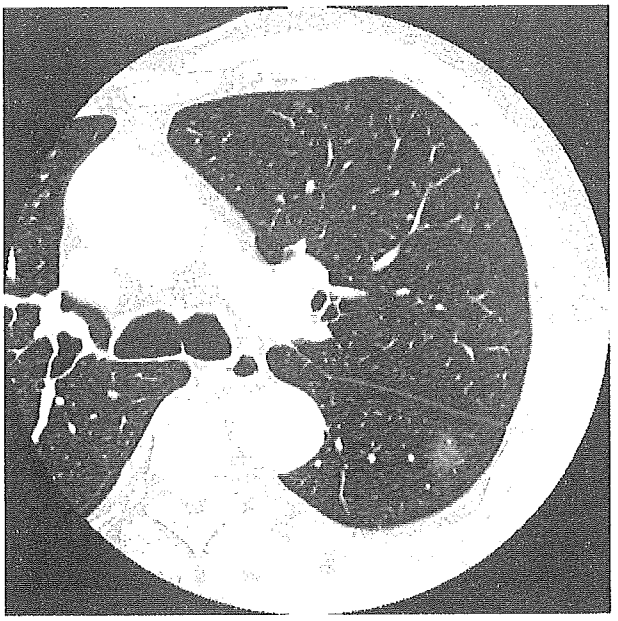

Fig 2. Type 1 tumor is homogeneous in density, and this tumor has been called "pure GGO" or "simple GGO." (GGO = ground-glass opacity.)

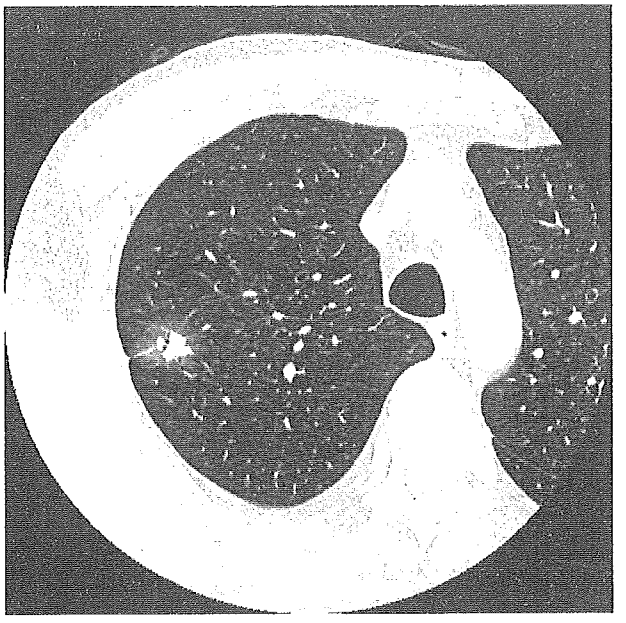

Fig 4. Type 3 tumor is heterogeneous in density, and the solid component comprises less than 50% of its diameter, and is composed of solid and surrounding GGO. (GGO = ground-glass opacity.)

were used to determine the combination of factors that were essential in predicting prognosis. Statistical analysis was considered to be significant when the probability value was less than 0.05. Although survival data are shown in this study, this information is considered to be merely suggestive because of the short median follow-up period (just 30 months) for the 341 surviving active patients.

Results

Clinical Characteristics by Radiologic Classifications

Patients with resected adenocarcinoma of the lung 2 cm or less in size were divided into six groups (Table 2). Type 1, 2, 3, 4, 5, and 6 tumors were found in 22 (5.9%), 26 (7.4%), 25 (7.2%), 43 (12.3%), 54 (15.5%), and 179 (51.3%)

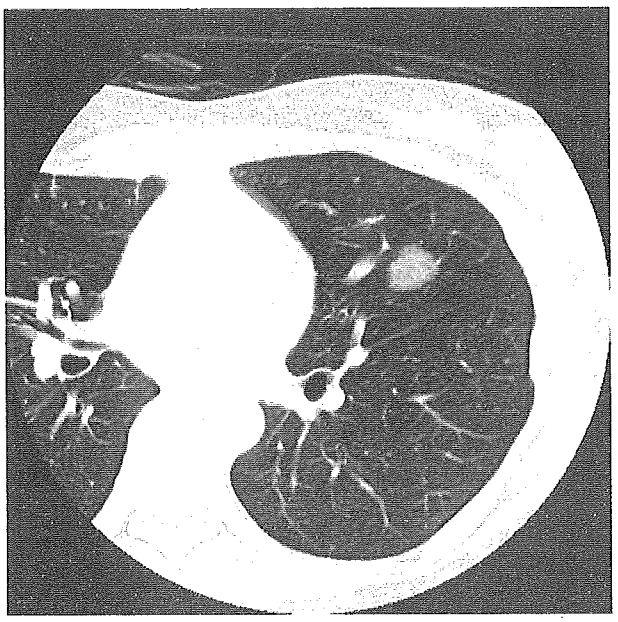

Fig 3. Type 2 tumor is homogeneous in density. It is too dense to call it "pure GGO." The density is much denser than type 1 tumor. (GGO = ground-glass opacity.)

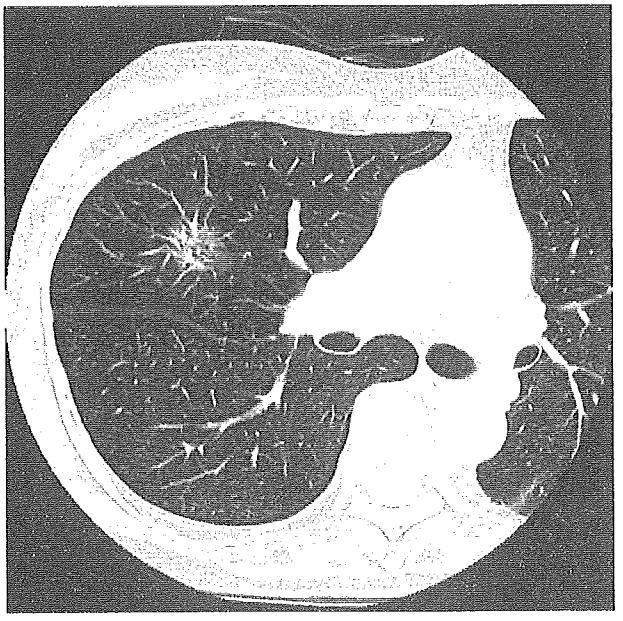

Fig 5. Type 4 tumor is heterogeneous in density, and the patterns of the solid component and GGO distinguish type 3 from type 4. (GGO = ground-glass opacity.)

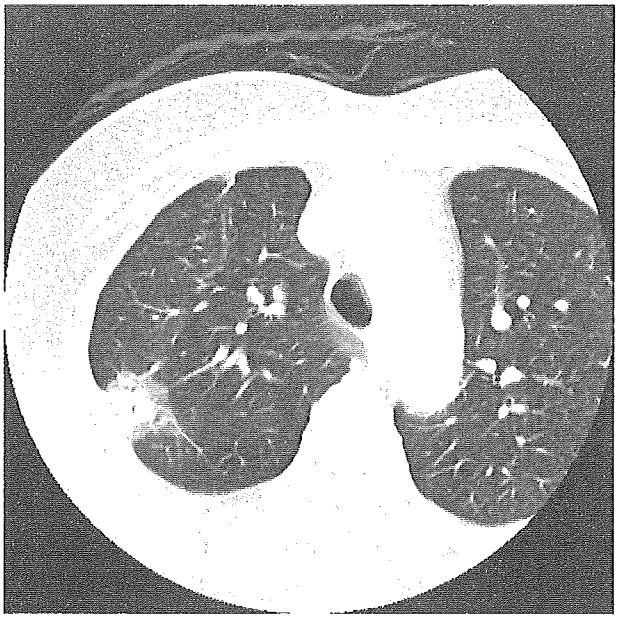

Fig 6. Type 5 tumor predominantly has a solid component and surrounding GGO. (GGO = ground-glass opacity.)

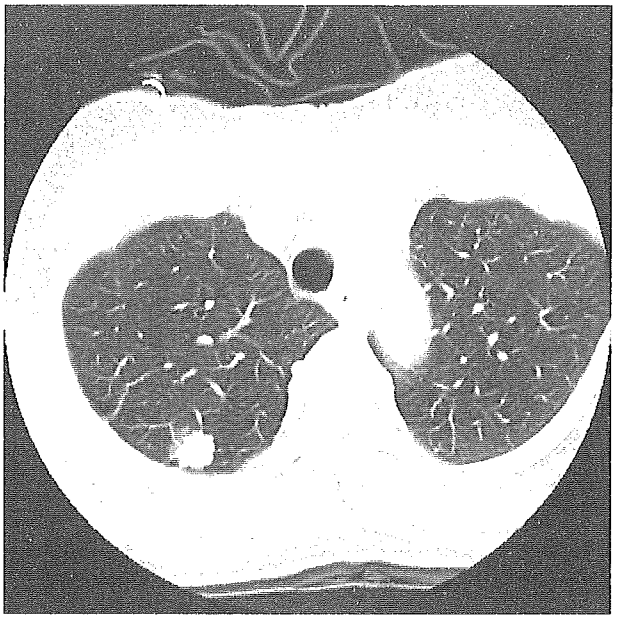

Fig 7. Type 6 tumors predominantly have a solid component. This tumor is so-called pure solid.

patients, respectively. With regard to sex differences, women outnumbered men in each category except type 6. The radiologic maximal tumor dimension ranged from 0.6 to 2.0 cm, with a mean of 1.5 cm, and there were no significant differences among the six categories. Although approximately 20% of patients with type 5 or 6 tumors did not have stage I disease, all but 1 patient with tumors in the other types had stage I disease ($p < 0.001$).

Pathologic Characteristics by the Radiologic Classifications

No nodal involvement was observed among patients with type 1, 2, or 4 tumors. One (4%) patient in type 3 had N1 disease, and 3 patients (5.6%) with type 5 tumors had nodal disease; one N1 and two N2. Type 6 tumors frequently metastasized to regional lymph nodes (43 [24%] patients). Lymphatic invasion was rarely found in patients with type 1, 2, 3, or 4 tumors, whereas this was frequently found in patients with type 5 or 6 tumors ($p < 0.001$). Similar findings were observed for vascular and pleural invasion (Table 3). There were 7 overall deaths, and all died of cancer. All of these patients had lung adenocarcinoma, which showed just a solid component on thin-section CT scan, ie, type 6 tumors. There were no deaths in patients in types 1 to 5, although the median follow-up period for surviving patients is just 30 months.

Table 2. Radiologic Classification and Clinicopathologic Features in Adenocarcinoma of the Lung

Variable	Type 1 Pure GGO	Type 2 SC	Type 3 Halo	Type 4 Mixed	Type 5 Solid & GGO	Type 6 Solid
Number of cases	22 (6.3%)	26 (7.4%)	25 (7.2%)	43 (12.3%)	54 (15.5%)	179 (51.3%)
Mean age (y)	58.6	56.4	64.1	62.3	62.9	62.9
Sex (men/women)	9/13	7/19	11/14	19/24	22/32	99/80
CEA > 5 ng/mL	1	0	1	3	3	40
Radiologic tumor size (cm)						
Range	0.6–1.9	0.8–2.0	0.8–1.9	0.9–2.0	0.9–2.0	0.8–2.0
Mean	1.2	1.4	1.5	1.4	1.5	1.5
Pathologic stage						
IA	21	25	24	43	51	130
IB	1	1	0	0	0	5
IIA	0	0	1	0	0	19
IIB	0	0	0	0	0	4
IIIA	0	0	0	0	2	18
IIIB	0	0	0	0	1	3
IV	0	0	0	0	0	0

CEA = carcinoembryonic antigen; GGO = ground-glass opacity; SC = semiconsolidation.

Table 3. Relationship Between Radiologic Classification and Pathologic Characteristics in Resected Adenocarcinoma of the Lung

Variable	Type 1 Pure GGO	Type 2 SC	Type 3 Halo	Type 4 Mixed	Type 5 Solid & GGO	Type 6 Solid
Total cases	22 (6.3%)	26 (7.4%)	25 (7.2%)	43 (12.3%)	54 (15.5%)	179 (51.3%)
pT1/pT2–T4	21/1	26/0	25/0	43/0	53/1	165/14
Lymph node metastasis	0 (0%)	0 (0%)	1 (4%)	0 (0%)	3 (5.6%)	43 (24%)
pN1/pN2	0/0	0/0	1/0	0/0	1/2	23/20
Skip metastasis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	7 (4.0%)
Lymphatic invasion	1 (5%)	0 (0%)	1 (4%)	0 (0%)	10 (18.5%)	84 (47%)
Vascular invasion	1 (5%)	0 (0%)	0 (0%)	1 (2%)	5 (9.3%)	86 (48%)
Pleural invasion	2 (9%)	0 (0%)	0 (0%)	1 (2%)	4 (7.4%)	48 (27%)

GGO = ground-glass opacity; SC = semiconsolidation.

Clinical Predictors for Nodal Involvement, N1 Disease, and Skip Metastasis

On the basis of multivariate analysis, preoperative carcinoembryonic antigen (nanograms per milliliter; continuous variable) and radiologic findings (types 1 through 4 versus types 5 and 6) were significant predictors for nodal involvement (Table 4). As to N1 disease, preoperative carcinoembryonic antigen (nanograms per milliliter; continuous variable), and radiologic findings (types 1 through 4 versus types 5 and 6) were again significantly associated with pathologic N1 disease (Table 5). None of the clinical factors were detected to be predictors for so-called skip metastasis.

Comment

Recent investigation of small adenocarcinoma of the lung has revealed the pathologic characteristics of these tumors detected by CT scan. Several authors insisted that the prognosis of lung adenocarcinoma with a large area of GGO on thin-section CT scan was much better than that of conventional adenocarcinoma of the lung regardless of the maximal tumor dimension (Table 6) [4, 9–15]. These reports provide interesting material for discussion. If adenocarcinoma with a good prognosis can be diagnosed preoperatively, major lung resection might not be required. Some authors have already adopted segmental resection for small-sized lung cancer, and have reported that it might be acceptable for patients with a tumor of 2.0 cm or less in diameter without nodal involvement [16, 17]. From these reports, a peripherally located lung cancer with no lymph node metastasis is the optimal indication for a more limited anatomic resection. However, it is difficult to determine the pathologic nodal status during surgical resection, and there could be some discrepancy between the results of intraoperative frozen-section diagnosis and the final pathologic diagnosis of lymph node metastasis. Locoregional recurrence has been noted after extended segmental resection, and it is possible that such local recurrence might have been prevented by pulmonary lobectomy. Thus, the preoperative diagnosis of the biologic invasiveness of a lung cancer is crucial whenever surgeons dare to adopt a lesser anatomic resection for a resectable lung cancer, which could raise the question of compromised patients.

According to previous data, lung adenocarcinoma with a large area of GGO shows a good prognosis, and one of the most important prognostic factors is the extent of GGO. However, how can the extent of GGO be evaluated in patients with type 4 adenocarcinoma? Inasmuch as type 4 tumor is made up of a heterogeneous mixture of GGO and a solid part, it is difficult to measure the size of the solid part. As a result, there is considerable disagreement among physicians on the diagnosis. Some may diagnose such tumors as "noninvasive," and others may diagnose them as "invasive" based on CT findings. The reason for this inconsistency is probably that the former radiologic classification is ill-suited for evaluating peripheral lung adenocarcinoma. The extent of GGO is insufficient for the evaluation of all adenocarcinoma of the lung. It may still be difficult for some surgeons to classify small adenocarcinoma of the lung based on our classification.

Among the six types of peripheral small-sized adenocarcinoma, women were predominant in all types except among patients with type 6 tumors. This is an unexpected finding. Traditionally, lung cancer is found more often in men than women. There was no significant difference among the types with regard to the maximal tumor dimension. Regarding small-sized adenocarcinoma of the lung, Noguchi and colleagues [6] investigated prognostic factors based on the findings of central fibrosis. They stated that type A or B tumors should be considered "in-situ" adeno-

Table 4. Results of Multivariate Analysis for Predictors of Nodal Involvement

Variable	Risk Ratio	95% Confidence Interval	*p* Value
CEA (continuous variable; ng/mL)	1.088	1.025–1.155	0.0059
Radiologic classification (type 1–4 vs 5–6)	0.057	0.008–0.427	0.0052

CEA = carcinoembryonic antigen.

Table 5. Results of Multivariate Analysis for Predictors of N1 Disease

Variable	Risk Ratio	95% Confidence Interval	*p* Value
CEA (continuous variable; ng/mL)	1.092	1.029–1.158	0.0037
Radiologic classification (type 1–4 vs 5–6)	0.074	0.010–0.554	0.0112

CEA = carcinoembryonic antigen.

carcinoma of the lung. It is probably safe to say that segmental resection or wide wedge resection is sufficient for such tumors because of their minimally invasive nature. Type 1 tumor is also known as pure GGO or simple GGO [18]. Among 22 type 1 tumors, there was no lymph node metastasis, and pathologic findings showed minimal invasion. There were 15 (68%) tumors that were equivalent to the type A or B tumors of Noguchi and colleagues [6], ie, roughly bronchioloalveolar carcinoma. Type 2 tumor is denser than type 1 tumor on thin-section CT scan. This tumor is not a solid tumor because we can see the underlying bronchovascular structure. No lymph node metastasis was noted, and 11 tumors were similar to the type A or B tumors of Noguchi and colleagues [6]. The difference in their density is probably related to the difference in the amount of air contained in the tumor, ie, differences in alveolar space histologically. Type 3 tumor is also known as GGO halo. One tumor had metastasized to the intrapulmonary lymph node, ie, N1 node, but 15 tumors were still diagnosed as being equivalent to the type A or B tumor of Noguchi and colleagues [6]. Type 4 tumor is actually defined by our original definition. This tumor consists of a mixture of GGO and a solid part containing air, roughly air-bronchogram. There was no lymph node metastasis and no lymphatic invasion. Basically, lung adenocarcinoma in the above four types is thought to be "minimally invasive" adenocarcinoma. A limited anatomic resection of the lung could be the standard surgical procedure for such tumors in the near future.

Type 5 and 6 tumors are considered to exhibit a "solid" course. Lymph node metastasis was found in roughly 5% of type 5 tumors, and 27% of type 6 tumors. Traditionally, lymph node metastasis is found in approximately 15% of small adenocarcinoma 2.0 cm or less in size. According to our results, however, lymph node metastasis was found mostly in type 6, which meant that if peripheral lung adenocarcinoma showed GGO on thin-section CT, the probability of lymph node metastasis was less than 5%. These "solid" tumors could be divided into several subgroups by means of positron emission tomography. If the solid tumors show positive results by positron emission tomography, they may be associated with a high frequency of lymph node metastasis and a poor prognosis.

One of the important objectives of this study is to determine the indication for limited surgical resection for lung adenocarcinomas. From this concept, the classification became simpler if the classification was composed with groups, ie, types 1 through 4 and types 5 and 6. If a tumor belongs to types 1 through 4, the patient would be a candidate for limited surgical resection, whereas a tumor belonging to group 5 or 6 warrants major lung resection with systematic lymph node dissection necessary. However, we believe the six classifications proposed in this study remain important for the surgeon to plan for the management of peripheral lung cancer. For instance, most of the type 1 tumors are bronchioloalveolar carcinoma, and some of them might be indolent tumors. On the contrary, type 2 tumors tend to be adenocarcinoma with invasive foci pathologically and grow in size. Actually we made a plan for a prospective follow-up study for type 1 tumors, not for type 2 tumors. Thus, clinical strategy depends on the six classifications, and we hope to leave the classification intact.

As to the surgical indications for pure GGO tumors, we resected the tumor if it is stable or increased in size. However, from our data, tumors belonging to type 1 could be bronchioloalveolar carcinoma, and are sometimes indolent. Thus, recently we just monitor such type 1 tumors without surgical interventions if the radiologic maximal

Table 6. Review of Literature Regarding Proportion of Ground-Glass Opacity as Radiologic Prognostic Factors in Adenocarcinoma of the Lung

Authors	Year	No.	Cases	Methods	Good Prognosis	Analysis
Jang et al. [9]	1996	14	...	...	Focal area of GGO	Univariate
Aoki et al. [4]	2001	127	Ad, cT1	Dimension	GGO > 0.5	Univariate
Kodama et al. [10]	2001	104	Ad, 2 cm or less	Visual	GGO > 0.5	Multivariate
Takamochi et al. [19]	2001	269	Ad, peripheral	TDR	TDR & CEA	Multivariate
Kim et al. [11]	2001	224	Ad, cT1	Visual	GGO extent	Univariate
Matsuguma et al. [12]	2002	111	Ad, cIA	Visual	GGO > 0.5	Univariate
Takashima et al. [15]	2002	64	Ad, 2 cm or less	CT	GGO > 0.57	Multivariate
Suzuki et al. [14]	2002	69	Ad, cIA	Dimension	GGO > 50%	Univariate
Okada et al. [17]	2003	167	Ad, cT1	TDR	TDR > 0.5	Multivariate
Ohde et al. [13]	2003	98	Ad, cT1	Dimension	GGO > 50%	Univariate

Ad = adenocarcinoma; CEA = carcinoembryonic antigen; cT1 = clinical T1; GGO = ground-glass opacities; TDR = tumor disappearance ratio.

tumor dimension is less than 15 mm. If radiologic findings suggest the tumor as lung cancer, preoperative CT-guided fine-needle biopsies are not always performed because of the high rate of a false-negative result for GGO tumors.

In conclusion, a new radiologic classification of small-sized adenocarcinoma of the lung has been proposed. Because this is the retrospective study, there may be numerous levels of bias. Therefore, we are planning to perform a prospective study of the management of peripheral small adenocarcinoma of the lung. Using the classification, we can easily classify peripheral adenocarcinoma of the lung into six categories, and the classification is significantly associated with pathologic prognostic factors. Future treatment strategies for small-sized adenocarcinoma of the lung may be based on this new radiologic classification.

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INVITED COMMENTARY

Anatomical resection is the standard treatment for early stage nonsmall cell lung cancer. As radiographic scanning methods are improving and we are identifying cancers at smaller sizes than previously recognized, the issue of limited resection for small peripheral cancers is being reinvestigated. Should small size on computed tomography (CT) be the only criteria with which to determine the type of resection (ie, anatomical versus limited [wedge]) to be performed? The answer would be no, according to the article by Suzuki and colleagues [1]. This study is a retrospective review of a single institutional experience in 349 chemotherapy–radiotherapy naive patients with small, single peripheral lung primary adenocarcinomas during a 4-year period of time from 1999 to 2003 to evaluate a new radiographic classification that may assist in the future management of patients. From their classification, in essence a radiologic Noguchi classification [2], they were able to identify a group of patients who might be best treated with limited resection. In their series, the 42 patients with either N1 or N2 disease seemed to have a greater solid component and less ground glass opacification (GGO) features than those who did not have those features. The authors concluded that their classification may be a useful evaluation system for future trials.

Some articles raise more questions than answers, as does this article. Clinicians should not be tempted to follow the authors' implications (given the retrospective design of this study) that thin-section CT peripheral lung

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6. Ⅲ期非小細胞肺癌の治療

(2) 外科の立場から

大阪市立総合医療センター呼吸器外科
多田 弘人
Hirohito Tada

はじめに

Ⅲ期についての定義は，結構複雑である。治療前の判定ではstage Ⅰ～Ⅱであったが，切除してみると病期Ⅲであったという場合もある。臨床病期がⅠ～Ⅱ期の場合には手術を先行するのが通常である。その後，術後化学療法を行うかどうかについては，本稿では省略する。

ここで求められているものは臨床病期Ⅲ期非小細胞肺癌である。しかし，臨床病期Ⅲといってもその定義も結構複雑である。なぜなら，CTスキャンでどれくらいの縦隔リンパ節腫大があればc-N2と診断してよいのか？ その場合，縦隔鏡はどれくらい必須か？ についてのコンセンサスはいまだに確定していないというのが現状であろう。筆者は図1くらいの大きさのリンパ節が腫大していれば，縦隔鏡なしでもN2と診断できると考えているが，臨床試験を行う上では病理検体による確認は必須であろう。最近では超音波ガイド下に針生検を行うという方法も報告されており，今後の診断方法の進歩が待たれる。

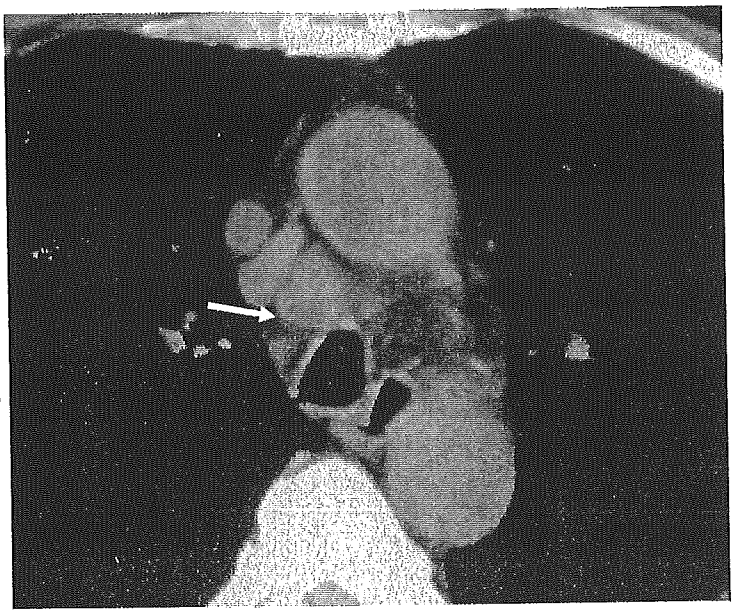

図1
気管前にリンパ節腫大を認める（矢印）。リンパ節は周辺への浸潤がなく切除可能と考えられる

本稿では，CTでN2と診断され，かつ切除可能であるとの判断がなされた症例を対象とした場合の治療法について考察を加えたい。

N2症例に対する外科手術（表1）

切除して初めてN2とわかった症例については，過去多くの報告が行われている。いずれの報告も切除単独の成績は13％程度と非常に悪い。切除例のなかでも治癒切除が行われた症例に限れば，その5年生存率は20～29％くらいである。しかし，切除前に縦隔リンパ節転移を縦隔鏡で証明した症例に対する切除単独の5年生存率は10％未満である[1]。これらの結果から，臨床病期ⅢAに対する切除単独の治療法は現在では容認されていない。

N2に対する術前化学療法（表2，3）

c-N2に対して，術前に化学療法を行うことがBurkeらのグループにより報告された。これに引き続いて，Martiniらは136例のN2症例に対して，Burkeらと同様のmitomycin＋vindesine＋CDDPの術前治療を行った。いずれも3年生存率が26～28％であり，従来のc-N2よりも良好で

表1　p-N2症例に対する手術成績

	報告者	症例数	5年生存率（%）
p-N2 all	Naruke	426	14
	Watanabe	199	13.5
治癒切除	Goldstraw	127	20
	Martini	151	29
	Naruke	252	19
	Mountain	118	21
	Watanabe	144	20
	Miller	147	24
縦隔鏡N2症例	Pearson	79	9
	Coughlin	28	18

表2　c-N2を対象としたinduction chemotherapyの2相試験

Source	Stage	n	chemotherapy	response rate	resection rate	MST (survival)
Burke	ⅢAN2 ⅢBN2	39	MVP × 2-3	64%	56%	19mo 26%：3yr
Martini	ⅢAN2	136	MVP × 2-3	77%	65%	19mo 28%：3yr
Darwish	ⅢAN2	46	PE × 2-3	82%	72%	24.5mo 53%：2yr
SAKK	ⅢAN2	90	PDoc × 2-ope-RT	66%	62%	23mo

表3　induction chemotherapyの比較試験

Source	Stage	n	chemotherapy	response rate	resection rate	MST (survival)
Rosell	ⅢAN2	30	MIP × 3-ope-RT	53%	77%	26mo
		30	ope-RT		90%	8mo
Roth	ⅢA	28	CEP × 3-ope-CEP	35%	39%	67mo
		32	ope		31%	11mo
Nagai	ⅢAN2	31	PV-ope	28%	65%	17mo
		31	ope		77%	16mo
Depierre	c-Ⅱ-Ⅲa	179	MIP-ope		94%	37mo
		176	ope		91%	26mo

あると報告された[2]。その後，いくつかの第Ⅱ相試験が行われたが，いずれも術前治療のfeasibilityが証明されたにすぎなかった。最近では新規抗癌剤のdocetaxelを用いた術前治療が行われ，生存期間中央値（MST）で23カ月と良好な結果であった。

1994年になって，2つの比較試験が報告された。いずれも手術単独と術前化学療法を比較したもので，中間解析により大きな差が生じたため，比較試験は症例集積を待たずに中止された。化学療法の奏効率は25～53%であり，Ⅱ相試験で認められた奏効率と矛盾しない結果であったが，症例数が両群で60例と非常に少ないため，必ずしも術前化学療法を標準的治療と認めるほどのインパクトはなかった。わが国では，JCOGが縦隔リンパ節転移陽性症例を対象に，手術単独と術前化学療法の比較試験を行ったが，これも登録ペースが悪く途中で中断された。登録症例数は同様に両群で62例であったが，両群のMSTは17カ月と16カ月であり，術前化学療法の有用性を証明することはできなかった。

2002年にDepierreらは両群で355例の術前化学療法と手術単独の比較試験を報告した。MSTは37カ月と26カ月であったが，統計学的有意差は得られなかった。とくにN2症例は化学療法と切除単独との間に予後の差はほとんど認められなかったが，N0-1症例について検討すると化学療法群のほうが良好であり，今後の臨床試験の方向性を示唆させる内容であった[3]。こうした検討がなされている間に，切除不能局所進行肺癌の治療の標準

表4　N2を対象としたinduction chemo-radiotherapyのII相試験

Source	Stage	n	chemotherapy	RT (Gy)	response rate	resection rate	MST (survival)
CALGB	IIIAN2	41	FVP×2	30	51%	61%	16mo
SWOG	IIIAN2	75	PE×2	45	69%	76%	13mo
	IIIB	51			45%	63%	17mo
Rice	IIIAN2	42	PE×1	27	57%	79%	21mo
	IIIB						
Choi	IIIAN2	42	PVF×2	42	73%	93%	28mo
							37%：5yr
Eberhardt	IIIAN2	94	PE×4	45		53%	31%：4yr
	IIIB						26%：4yr

は，放射線化学療法であることがしだいに鮮明になってきた。

術前放射線化学療法(表4)

IIIA～IIIB症例に対する放射線化学療法は有効性が証明されてはいるものの，放射線化学療法の開始時期や，その後の維持療法をどうするかについてなどいまだ問題は山積している。SWOGではdocetaxelを維持療法に用いるとよいと報告している[4]。一方で，より局所効果を図るために放射線化学療法に引き続いて切除をすることがいくつか試みられた。放射線を加えることによって，奏効率はいずれも向上したが，手術を加えたことが生存にどれほど効果がもたれるかについてはII相試験からでは明確な答えを出すことはできない[5]。

アメリカでは，CDDP＋VDSにradiation 45Gyを同時併用したのち，booster radiationを61Gyまで加えるものと切除を加えるものを比較する試験が行われた[6]。510例を目標にしていたが，集積が遅いために429例で登録を終了した。無再発生存は切除群のほうが良好であったが，全体の生存では両群の予後に差は認められなかった。この大きな理由は，手術群のほうで治療関連死亡が5%(14/201 vs. 7/191)多く発生したためと考えられる。この結果についての考察は非常に難しい。無再発生存が良好であったとしても全体の生存で差が認められなかった以上，手術を追加する意味は少ないと考えられる。しかし，治療関連死亡のうちの12例までが一側肺全摘であることを考慮すると，もし肺全摘を回避できていたら生存でも有意差を見い出すことができたかもしれない。

一方で，T4N0症例やパンコースト腫瘍については放射線化学療法後に切除をすることがおそらく有効であると考えられている[7]。これらの腫瘍はリンパ節転移を伴わないため，局所制御が治療の根幹になると考えられる。しかし，症例数が少ないために比較試験を行う対象とはならず，II相試験の結果から標準治療であると考えられるに至っている。

今後の展開

近年，分子標的薬が画期的効果を上げつつあるため，今後は術前治療にこれらの薬剤を併用することが行われるであろう。また，induction therapy後に脳転移が頻発することから予防的脳照射の成績も今後示されるものと思われる。また，術前治療として新規抗癌剤が用いられるようになってきているが，放射線を切除前に投与するか術後投与するか，それとも，術前は抗癌剤だけのほうがよいのかについても，今後の臨床試験の結果が待たれる。

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ORIGINAL REPORT

Neuroendocrine Neoplasms of the Lung: A Prognostic Spectrum

Hisao Asamura, Toru Kameya, Yoshihiro Matsuno, Masayuki Noguchi, Hirohito Tada, Yuichi Ishikawa, Tomoyuki Yokose, Shi-Xu Jiang, Takeshi Inoue, Ken Nakagawa, Kinuko Tajima, and Kanji Nagai

From the National Cancer Center Hospital; The Cancer Institute Hospital, Tokyo; National Cancer Center East, Chiba; Shizuoka Cancer Center, Shizuoka; Kitasato University School of Medicine, Kitasato; Tsukuba University School of Medicine, Tsukuba; Sanritsu Co, Chiba; and Osaka City General Hospital, Osaka, Japan.

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Address reprint requests to Hisao Asamura, Division of Thoracic Surgery, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan; e-mail: hasamura@ncc.go.jp.

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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