Objective radiologic analysis of ground-glass opacity aimed at curative limited resection for small peripheral non-small cell lung cancer

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Objective: The aim of this study was to evaluate the efficacy of the objective radiologic analysis of high-resolution computed tomographic images of small peripheral non-small cell lung cancer and to select the candidates for curative limited resection.

Methods: High-resolution computed tomographic images of 146 surgically resected T1 N0 M0 peripheral non-small cell lung cancers were analyzed by using National Institutes of Health image software and classified on the basis of the percentage of ground-glass opacity within the tumor.

Results: Eighty-seven percent of tumors with ground-glass opacity ratios of 90% to 100% (type I) were diagnosed as noninvasive bronchioloalveolar carcinoma, whereas 55.6% of tumors with ground-glass opacity ratios of 50% to 89% (type II) consisted of adenocarcinoma. Tumors with ground-glass opacity ratios of 50% or more (type I/II) had no nodal involvement, whereas nodal metastases were identified in 20.0% of tumors with ground-glass opacity ratios of 10% to 49% (type III) and 24.4% of tumors with ground-glass opacity ratios of less than 10% (type IV). No tumors with ground-glass opacity ratios of 50% or more showed vessel infiltration, except for one lesion with a ground-glass opacity ratio of 50%. The 3-year disease-free survival was 97.7% for type I/II, 86.1% for type III, and 78.5% for type IV tumors.

Conclusions: The objective quantitative radiologic analysis with National Institutes of Health image software exhibited a good correlation with the histologic classification, pathologic invasiveness, and postoperative outcome of small peripheral lung cancer. Patients with tumors that have ground-glass opacity ratios of greater than 50% are considered to be possible candidates for limited pulmonary resection.

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With recent advances in low-dose helical computed tomography (CT), the detection of small peripheral lung cancer has been notably increasing.¹⁻⁵ A majority of the CT-detected lung cancers are adenocarcinomas, which often show ground-glass opacity (GGO) on a high-resolution CT (HRCT) image. GGO is caused by alveolar lining tumor growth with an increase in the thickness of the alveolar septa, and it corresponds to the bronchioloalveolar carcinoma (BAC) component of the tumor.⁶ Several previous studies reported that the percentage of GGO area within a tumor was a prognostic factor in peripheral lung adenocarcinoma.⁷⁻⁹ These reports

Figure 1. A, An HRCT image of small peripheral adenocarcinoma. B, By using NIH image software, the HRCT image was transformed into 20 optional colors according to the CT numbers of each pixel. The GGO percentage was calculated by tracing the colors corresponding to the GGO area.

demonstrated that tumors with GGO ratios of larger than 50% in the maximum dimension on HRCT image were minimal or no invasive adenocarcinomas, which exhibited an excellent postoperative outcome. Although the results suggested that tumors with large GGO ratios could be likely candidates for limited pulmonary resection for cure, the adequate criteria for selecting patients for limited resection are still controversial. One of the reasons for the controversy is limited objectivity in the radiologic evaluation of the GGO ratio. Although GGO is defined as hazy increased attenuation of the lung without obscuration of the underlying vascular markings,¹⁰ most of the previous studies were based on the results of the macroscopic measurement of the GGO ratio on HRCT imaging. Unless an objective method to measure the GGO percentage is established, the results are different among individuals, and the liberal application of limited pulmonary resection might result in an increased risk of local or early recurrences. In this study we used National Institutes of Health (NIH) image software to establish an objective radiologic analysis of small peripheral lung cancer. NIH image software is a public domain, image-processing, and objective analysis program developed at the NIH in the United States. The aim of this study was to evaluate the efficacy of the objective radiologic analysis with NIH image software and to select the appropriate candidates for limited resection among the patients with small peripheral non-small cell lung cancer (NSCLC).

Patients and Methods

Patients

From January 1999 through December 2001, 280 patients with NSCLC underwent pulmonary resection at National Shikoku

Cancer Center. Of these, 146 patients were classified as having clinical stage IA peripheral-type lung cancer. Staging procedures included HRCT of the chest, ultrasonography of the upper abdomen, magnetic resonance imaging of the brain, and bone scintigraphy. Lymph nodes smaller than 10 mm along the short axis on the CT scan were defined as negative nodes. Preoperative analyses of the HRCT images were performed with NIH image software for these 146 consecutive patients. The subjects included 68 men and 78 women with a median age of 64.9 years (range, 38-87 years). Surgical procedures were selected on the basis of the performance status, pulmonary function, and HRCT findings of the lesions. As described in our previous report,¹¹ limited resection was adopted prospectively for tumors with a pure GGO appearance on HRCT since June 2000. The surgical procedures performed were as follows: lobectomy with systematic mediastinal dissection in 103 patients, segmentectomy with hilar sampling in 7 patients, and wedge resection in 36 patients. Histologic diagnoses were made according to the recent World Health Organization histologic classification.¹² The histologic type was BAC in 44 patients, adenocarcinoma in 87 patients, squamous cell carcinoma in 13 patients, and large cell carcinoma in 2 patients.

Radiologic Analysis With NIH Image Software

CT scanning was performed on a Somatom Plus 4 (Siemens Medical Systems, Malvern, Pa), and the images were photographed by using a window level of -500 Hounsfield units and a window width of 1500 Hounsfield units. The lesions were subject to scanning with 2-mm-thick sections at one breath hold. Preoperative analyses with NIH image software were performed on the HRCT image at the maximum dimension of the lesion. The image was transformed into 20 optional colors according to the CT numbers of each pixel within the lesion (Figure 1). In this study

TABLE 1. Patient characteristics

	Type I (n = 23)	Type II (n = 45)	Type III (n = 33)	Type IV (n = 45)
Sex (male/female)	8/15	18/27	14/19	28/17
Smoking (+/−)	5/18	15/30	17/16	28/17
Age (y)	63.1 ± 8.2	62.6 ± 10.6	62.6 ± 9.6	69.7 ± 8.3
Tumor size (mm)	12.0 ± 6.4	16.7 ± 6.4	21.0 ± 6.1	21.7 ± 6.7
Resection				
Lobectomy	7	28	29	39
Segmentectomy	1	3	1	2
Wedge	15	14	3	4

GGO was defined as the area with a CT number less than that of the intrapulmonary vascular structure. After the circumference of the lesion was traced, the GGO percentage within the lesion was calculated by tracing the colors corresponding to the GGO area. On the basis of the GGO percentage, all the tumors were classified into 4 categories: those with GGO percentages of 90% to 100% (type I), 50% to 89% (type II), 10% to 49% (type III), and 0% to 9% (type IV).

Statistical Analysis

Data were analyzed by using the Student unpaired *t* test and the χ^2 test. Survival time was calculated from the date of the operation. Cumulative survival rates were calculated by using the Kaplan-Meier method and analyzed with the log-rank test. A multivariate analysis was carried out by using the Cox proportional hazards regression model.

Results

Of 146 patients, 23 had type I tumors, 45 had type II tumors, 33 had type III tumors, and 45 had type IV tumors. Patient characteristics of each group are shown in Table 1. The patients with type IV tumors included a significantly larger number of male subjects and smokers than the patients with type I/II tumors ($P = .025$). The mean tumor size of type I/II tumors was significantly smaller than that of type III/IV tumors (type I vs type III/IV, $P < .0001$; type II vs type III, $P = .0038$; type II vs type IV, $P = .0006$). The histologic diagnoses of each group are shown in Table 2. BAC accounted for the majority of type I tumors (20/23 [87.0%]), whereas adenocarcinoma accounted for 55.6% (25/45) of type II and 90.9% (30/33) of type III tumors. All the lesions of squamous cell carcinoma and large cell carcinoma were included in type IV.

Wedge resection was performed in 15 patients with type I, 14 with type II, 3 with type III, and 4 with type IV tumors. Of those, 10 patients with type I and 12 with type II tumors who were given diagnoses of a pure GGO appearance by means of the macroscopic evaluation of HRCT images underwent intentional wedge resection according to our prospective study since June 2000. Segmentectomy was performed in 1 patient with type I, 3 with type II, 1 with

TABLE 2. Histopathologic findings

	Type I (n = 23)	Type II (n = 45)	Type III (n = 33)	Type IV (n = 45)
Histologic subtype				
BAC	20	20	3	1
w/d adenocarcinoma	3	22	20	4
m/d adenocarcinoma	0	2	9	18
p/d adenocarcinoma	0	1	1	7
Squamous cell carcinoma	0	0	0	13
Large cell carcinoma	0	0	0	2
pN status				
N0	8	31	24	31
N1	0	0	2	4
N2	0	0	4	6
NX	15	14	3	4
Vessel infiltration				
Negative	23	44	21	11
Positive	0	1	12	34

BAC, Bronchioloalveolar carcinoma; w/d, well-differentiated; m/d, moderately differentiated; p/d, poorly differentiated.

type III, and 2 with type IV tumors. Thirty-nine patients who underwent lymph node dissection or sampling for type I/II tumors had no nodal involvement, whereas lymph node metastases were identified in 20.0% (6/30) of patients with type III and 24.4% (10/41) of patients with type IV tumors (type I/II vs type III, $P = .0008$; type I/II vs type IV, $P < .0001$). Of those with lymph node involvement, 4 patients with type III tumors (13.3% [4/30]) and 6 patients with type IV tumors (14.6% [6/41]) had N2 disease. None of the patients with type I/II tumors showed vessel infiltration, except 1 patient, whose GGO ratio was 50.0%, whereas 36.4% (12/33) of patients with type III tumors and 75.6% (34/45) of patients with type IV tumors had vascular invasion ($P < .0001$).

At the median follow-up period of 24.5 months, 3 patients had died. Two patients with type IV tumors died from tumor progression, and one with a type III tumor died of cerebral infarction, although there was no recurrence of the tumor. The 3-year overall survival of all patients was 97.5%. The 3-year disease-free survival was 97.7% for patients with type I/II tumors ($n = 68$), 86.1% for patients with type III tumors ($n = 33$), and 78.5% for patients with type IV tumors ($n = 45$; Figure 2). Patients with type IV tumors showed a significantly poorer disease-free survival than patients with type I/II tumors ($P = .025$). All the patients with type I tumors were alive without any recurrences, whereas one patient with a type II tumor who underwent wedge resection because of a poor pulmonary reserve for a tumor with a GGO ratio of 50.0% had a relapse at the surgical margin.

Univariate analyses of disease-free survivals by several prognostic factors, including sex, smoking history, tumor

Figure 2. The disease-free survival curves for patients with small peripheral NSCLC according to the GGO percentage of the lesion. The 3-year disease-free survival rate was 97.7% for patients with type I and type II tumors ($n = 68$), 86.1% for patients with type III tumors ($n = 33$), and 78.5% for patients with type IV tumors ($n = 45$).

size, and the GGO percentage, are summarized in Table 3. There was a significant difference in the disease-free survival between the patients with a GGO ratio of 50% or greater and those with a GGO ratio of less than 50%, whereas no significant differences were found in other variables. The multivariate analysis also demonstrated that the GGO percentage calculated with NIH image software was a significant predictor of a favorable disease-free survival (Table 4).

Discussion

In 1995, the Lung Cancer Study Group reported a higher incidence of locoregional recurrence after limited resection for T1 N0 lung cancer compared with that after lobectomy.¹³ On the basis of the results, lobectomy with systemic mediastinal lymphadenectomy is considered the standard treatment for patients with early-stage NSCLC. However, with the increasing detection of peripheral small lung cancer, there is a growing need for an adequate treatment strategy for small NSCLC. Several studies have demonstrated various predictive factors of peripheral small adenocarcinoma, which accounted for the majority of CT-detected lung cancers. Higashiyama and associates¹⁴ found an excellent prognosis of the tumor consisting of a BAC component of 100% when compared with that of tumors with a lesser BAC component. Suzuki and coworkers¹⁵ reported a 100% survival in patients

with adenocarcinomas with a central fibrosis of 5 mm or smaller. Although these results are useful to predict a good prognosis, candidates for curative limited pulmonary resection cannot be selected on the basis of these prognostic factors because the quantitative analyses for the predictive values are possible only by means of postoperative pathologic examination but not preoperatively. Kodama and colleagues⁷ studied the relevance of radiologic findings of small adenocarcinoma to pathologic studies and demonstrated that a GGO ratio of greater than 50% on HRCT images was a preoperative indicator of a favorable outcome. Matsuguma and associates¹⁶ also reported that the adenocarcinoma with a higher proportion of GGO area ($\geq 50\%$) had neither lymph node metastasis nor lymphatic invasion. This novel radiologic classification provided an insight into the possibility of selecting an adequate candidate for curative limited resection for small peripheral adenocarcinoma. However, there still remain some controversies to be determined. Of these, one of the essential problems concerns the limited objectivity in the radiologic evaluation of the GGO ratio. The macroscopic measurement of the GGO ratio on HRCT images is so subjective that individual variations can easily occur, and any overestimation could increase the risk of local recurrence and poor outcome after limited pulmonary resection. A few attempts were already made at an objective radiologic analysis for small adenocarcinoma. Nomori and coworkers

TABLE 3. Univariate analyses of prognostic factors

Variables	Unfavorable	Favorable	P value
Sex	Male	Female	.079
Smoking history	Yes	No	.218
Tumor size	> 15 mm	≤ 15 mm	.212
GGO percentage	< 50%	$\geq 50\%$	.010

GGO, Ground-glass opacity.

TABLE 4. Multivariate analyses of prognostic factors

Variables	Risk ratio	95% CI	P value
Sex	2.57	0.82-6.71	.120
Smoking history	1.52	0.14-1.78	.412
Tumor size	1.74	0.15-3.57	.735
GGO percentage	1.11	0.98-1.30	.056

CI, Confidence interval; GGO, ground-glass opacity.

ers¹⁷ reported the usefulness of a histogram analysis of CT numbers. Matsuguma and colleagues¹⁸ showed the validity of measurement of GGO ratio with Scion Image (Scion Corporation, Frederick, Md). In this study we used NIH image software for an objective radiologic evaluation of the GGO ratio to select the appropriate candidates for limited resection. NIH image software is freely available from the respective Web site. We think that studying the validity of widespread basic software is useful for future trials and clinical practice.

The recognition of the GGO area becomes easy and objective by means of analysis with NIH image software because the CT numbers of each pixel are expressed by 20 optional colors. The classification on the basis of the GGO percentage calculated with NIH image software exhibited a good correlation with the histologic classification, pathologic invasiveness, and postoperative outcome. Eighty-seven percent of type I tumors (GGO of 90%-100%) were diagnosed as being noninvasive BAC, and no vessel infiltrations were identified in all 23 lesions. All the patients with type I tumors were alive without any recurrences to date. Type I tumors corresponded to the lesions described as pure GGO in the previous reports. Our current study verified the reports that demonstrated a good prognosis of pure GGO.¹⁹⁻²² Fifty-five percent of type II tumors (GGO of 50%-89%) constituted adenocarcinoma, whereas there was no lymph node involvement in 31 patients who underwent node sampling or dissection, and no vascular invasion was identified in any of the 45 lesions, except for in 1 lesion with a GGO of 50%. On the contrary, 22.5% (16/71) of patients with type III and IV tumors revealed lymph node metastases regardless of the tumor size, and patients with type IV tumors showed a significantly poorer disease-free survival than patients with type I and II tumors. These results showed that it was the most appropriate for selecting treatment strategies to classify peripheral small lung cancers into 3 categories on the basis of GGO ratios of 90% to 100%, 50% to 89%, and 0% to 49%. Patients with tumors having GGO ratios of 90% to 100% can be considered as the most appropriate target for limited resection because the great majority of the tumors in this category are noninvasive. In these cases even observation without any surgical intervention would be one of the choices because BAC was reported to have a tumor doubling time of more than 1 year.²³ Tumors with GGO ratios of less than 50% have invasive features, and lymph node involvement was not uncommon. It has been shown that 10% to 20% of lung cancers of 2 cm or less in size have lymph node metastasis,^{24,25} and our results of patients with type III or IV tumors were comparable with the data. Standard anatomic resection with systemic mediastinal lymph node dissection is inevitable, even for a

small lung cancer with a GGO ratio of less than 50%. On the other hand, tumors with GGO ratios of 50% to 89% comprise the most heterogeneous group. Although the majority of tumors in this category were pathologically diagnosed as invasive adenocarcinoma, the minimal vascular infiltration and negative lymph node metastases in our series suggested that patients with tumors with GGO ratios of 50% to 89% could also be candidates for curative limited pulmonary resection, such as segmentectomy or even regional wedge resection. Further randomized studies are warranted to confirm the hypothesis obtained from our small series. However, we believe that an equivalent prognosis after limited resection could be expected by strict patient selection on the basis of an objective quantitative radiologic analysis.

When designing a prospective study, it is critically important to decide the threshold of the GGO percentage for assigning the patient to limited surgical intervention. Previous reports on the basis of the macroscopic estimations suggested that GGO ratios of greater than 50% were required for a patient to qualify as a candidate for limited resection. It should be noted that the similar results were obtained in our study on the basis of the objective radiologic analysis. However, even in our small series, one patient with a GGO ratio of 50% exhibited vessel infiltrations and experienced local recurrence after wedge resection. The limit of the GGO percentage for assignment to limited surgical intervention should be more than 50%, for instance 60% or 70%, to guarantee the ethics and safety of a prospective study. When such strict criteria are required to select the eligible patients, a subjective macroscopic evaluation is useless, and the lack of a method of objective quantitative radiologic analyses has prevented a large-scale multicenter trial. We believe that NIH image software will play an important role for selecting the eligible patients for the future clinical trials, as well as for deciding the treatment strategy at clinical practice.

In conclusion, appropriate patients for limited resection could be selected on the basis of the objective radiologic evaluation. Radiologic analysis with NIH image software exhibited a good correlation with the histologic classification, pathologic invasiveness, and postoperative outcome of small peripheral lung cancer. Patients with tumors having GGO ratios of larger than 50% are considered to be possible candidates for limited pulmonary resection. Further studies should be encouraged, with strict criteria on the basis of an objective quantitative radiologic evaluation.

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