Pulmonary Ground-Glass Opacity (GGO) Lesions–Large Size and a History of Lung Cancer are Risk Factors for Growth

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Objective: Ground-glass opacity (GGO) of the lung is being frequently detected by thin section computed tomography scan. However, the long term management of detected GGO is still unclear. To establish follow-up plans, we performed the clinical and radiological review to identify the factors that are closely associated with GGO growth.

Methods: We retrospectively analyzed computed tomography images of 125 GGOs that were stable for 3 months between 1999 and 2006 at the Cancer Institute Hospital, Tokyo. To identify factors that affect the roentgenological growth, the time to GGO growth curve by Kaplan-Meyer method was evaluated in terms of gender, age, smoking, initial size, existence of a solid part, GGO density, location, multiplicity, and lung cancer history by univariate and multivariate analyses.

Results: The median observation period was 1048 days (177–3269) and 26 of 125 GGOs (21%) grew. The estimated growth population for 5 years was 30%. The growth was more frequently seen in the elderly ($p = 0.017$), in part-solid GGO ($p < 0.01$) and in GGO of larger than 10 mm ($p < 0.01$, logrank test). By multivariate analysis, initial size ($p < 0.01$, Cox's model) and history of lung cancer ($p = 0.017$, logistic model) were independent factors that were significantly associated with GGO growth. Fifty GGOs that were 10 mm or smaller and without a lung cancer history did not grow within 3.5 years.

Conclusions: After initial management and 3 month follow-up, larger size (more than 10 mm) and a history of lung cancer are risk factors for GGO growth, and therefore should be considered when making a follow-up plan.

Key Words: Lung Adenocarcinoma, Ground-glass, Follow-up, Thin-section CT.

(*J Thorac Oncol.* 2008;3: 1245–1250)

Recent studies have demonstrated that screening with low-dose computed tomography (CT) can improve detection of lung cancer at an early and potentially curable stage.[1,2] Since CT screening has become more widely accepted and with advances in technique, very faint and smaller lesions called ground-glass opacities (GGOs) are now frequently encountered. GGO is a roentgenological term for lesions in the lung on thin section CT (TSCT), defined as a homogeneous hazy increase in density in the lung field that does not obscure the bronchiolovascular structure.[3,4] Recently GGOs were found in 0.2 to 0.5% of screened populations.[5] Pathologically, localized GGOs existing for months have been reported to correspond to precancerous lesions or early stage adenocarcinomas.[6–10] These pathologic conditions include atypical adenomatous hyperplasia (AAH) and bronchioloalveolar carcinoma (BAC) which replace alveolar epithelial cells according to the World Health Organization definition.[11] Although GGOs are generally reported to grow slowly, details of natural history remain limited.[12,13]

In this study, we therefore examined GGOs and part-solid GGOs that existed for more than 3 months on chest TSCT in our hospital. The purpose was to clarify factors that are likely to affect the growth of a GGO and to gain a better understanding to facilitate appropriate GGO follow-up planning.

PATIENTS AND METHODS

Patients

Between 1999 and 2006, 184 patients were referred to the Department of Thoracic Surgical Oncology, the Cancer Institute Hospital, Tokyo, for further examination of lung lesions that seemed as a GGO on chest TSCT. Among these, 17 patients (9%) had an immediate diagnostic work-up including surgical intervention and 10 patients were lost to

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Supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, from the Japan Society for the Promotion of Science, and by grants from the Ministry of Health, Labour and Welfare, the Smoking Research Foundation, and the Vehicle Racing Commemorative Foundation.

Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/08/0311-1245

follow-up. Although the remaining 157 patients were then followed-up for 3 months by CT scan, it was terminated in 32 patients for the following reasons (number of patients); vanished, (6) gross growth, (3) rapid increase in number and recognition as pulmonary metastasis, (4) advance in other malignancy, (1) patient's request, (3) and lost to follow-up. (11) TSCT was repeated and 125 patients, who showed no change in the repeat CT images, were finally enrolled in the study. Their clinicopathologic background and CT findings are shown in Table 1. Although 45 patients (36%) had multiple GGOs (range of number, 2–20), we only considered the largest lesions. Follow-up consisted of periodic TSCT at a 6-month intervals. The mean observation period was 1048 days (ranged, 177–3269), and follow-up CT scans were performed an average of 6 times in each case. In 59 cases, GGOs were detected at a health check-up or were found incidentally, and the others were detected during follow-up of prior malignancy (51 patients with lung adenocarcinoma (stage I, 48; stage II, 1; stage III, 2), 9 with breast cancer, 2 with gynecologic cancer, 2 with urologic cancer, and 2 with sarcomas). Nine patients with a history of lung cancer also had other cancers in other organs. The interval between the prior malignancy treatment and detection of the current GGO varied from 0 to 168 (mean 36) months among these 66 patients.

TABLE 1. Patient Background and CT Findings

	Total $n = 125$	With Growth $n = 26$ (%)
Patient background		
Gender		
Men	51	13 (25)
Women	74	13 (18)
Age (36–88, mean 62)		
≤60	44	5 (11)
60<	81	21 (26)
Smoking habit		
Never	58	10 (17)
Ever	41	10 (24)
Unknown	26	6 (23)
History of lung cancer		
Without	74	11 (15)
With	51	15 (29)
CT findings		
Initial size (3–17 mm, mean 8.3)		
≤10	87	8 (9)
10<	38	18 (47)
Existence of solid part		
Without (GGO)	95	14 (15)
With (part-solid GGO)	30	12 (40)
CT density (−810 to −10 HU)[a]		
≤−500	67	10 (15)
−500<	58	16 (28)
Location[b]		
Above	79	19 (24)
Below	46	7 (15)
Multiplicity		
Solitary	80	17 (21)
Multiple	45	9 (20)

[a] The mean CT density (HU) of 3 spots within the GGO.
[b] With reference to the major fissure of the lung.
GGO, ground-glass opacity; CT, computed tomography.

This retrospective study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Radiologic Definition of GGOs and Their "Growth" on TSCT

CT scan was performed with a GE Yokogawa Medical System, Light Speed QXi or High Speed DXi (Hino, Tokyo). For screening of the whole lung field, the scanning parameters were as follows: 120 kV, 230 mA, beam width of 7.5 mm, rotation speed of 1 revolution/s, table speed of 15 mm/s (pitch 2:1), and a reconstruction interval of 7.5 mm. When the presence of GGO was suspected, targeted axial scanning was repeated only for the suspected area based on the previous scanning. The scanning parameters were 120 kV, 280 mA (or 180 mA), clustered axial scanning of 1.25 mm or 2.0 mm slice and the largest diameter of the lesion was evaluated at WL-585HU and WW1800HU.[14] All scans were obtained in full inspiration without any contrast material and viewed in cine format on a computer workstation. All radiologic images were evaluated by 2 of the specialists who had 5 and 17 years of experience (MH, YS), respectively and a final consensus was obtained by plenary reading. The size of each lesion was recorded by evaluating the largest diameter using a caliper tool in the software. In this study, we discriminate "part-solid GGO" from "GGO." The definition of them was based on that of Henschke et al.,[15] in which the subcategories "nonsolid" and "part-solid" were recognized according to the absence/presence of solid parts in the GGO lesion. We prefer the term "GGO" to "nonsolid nodule" because a finding of GGO on TSCT corresponds specifically to a pathologic alveolar condition with noninvasive tumor-spreading, while "nonsolid nodule" does not. The remainder (24%) had a solid part, the diameter of which as a proportion of the diameter of the whole lesion was (solid part/ GGO) from 0.13 to 0.42 (2/16 mm–2.5/6 mm) and we used the term "part-solid GGO" for them in this study. All GGOs with extra findings (6 GGOs with cystic components and 12 GGOs with heterogeneous ground-glass density) were included as "GGO." The "CT density" was defined as the mean density (HU) measured at three spots within the GGO part of each lesion with the software tool. "Growth" of a GGO was concluded when any of the following were recognized: gross increase in the greatest dimension by at least 2 mm from the initial TSCT (Figure 1), gross increase in the size of the solid part by at least 2 mm, or a new solid part of any size (Figure 2).

Statistical Analysis

The follow-up time was defined from the date of the initial TSCT to the latest TSCT. To clarify the factors that may affect GGO growth, univariate and multivariate analyses were performed with regard to the growth incidence (numbers of GGO with concluded growth/numbers at risk). In this retrospective investigation, multivariate analyses were ap-

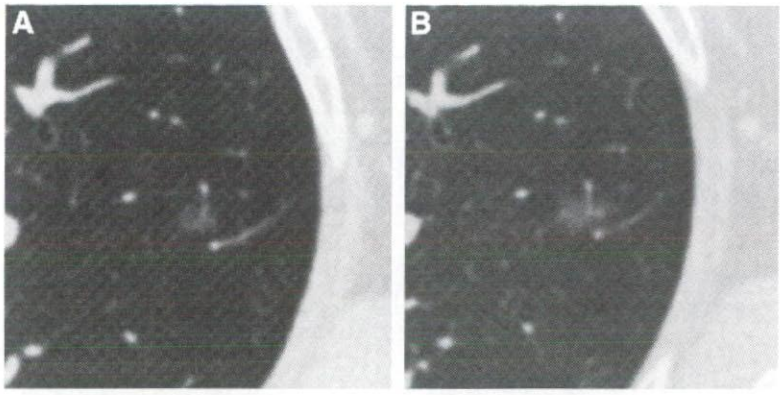

FIGURE 1. A case showing GGO increase in size. (*A*) GGO in the left upper lobe, measuring 7 mm in diameter at detection. (*B*) Growth by 3 mm was confirmed after 10 months.

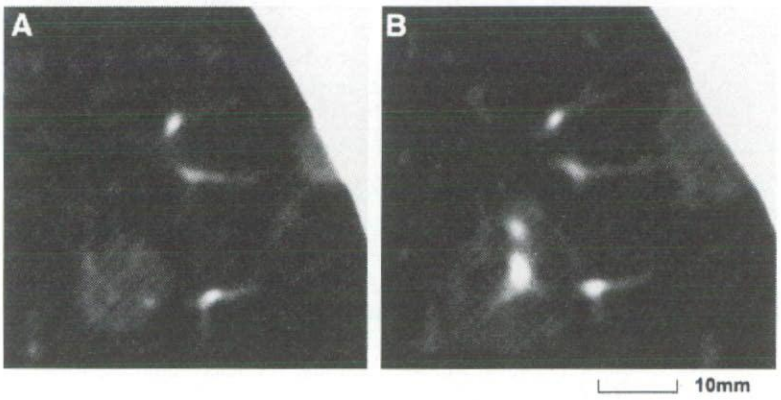

FIGURE 2. A case with GGO increase in size and formation of a solid part. (*A*) 9 mm and 7 mm GGOs detected in the left upper lobe. (*B*) Growth in size (to 17 and 12 mm, respectively) and became part-solid GGO after 7 months.

plied for two separate studies: one to evaluate the time to GGO growth and the other to evaluate GGO growth incidence. For the first, the time to GGO growth curves were estimated by the Kaplan-Meier method, and the difference of the time to GGO growth curve between each group was tested by the log-rank test. Independent variables that influenced the time to GGO growth were analyzed by Cox's proportional hazard model. For the analysis, the original continuous variables, such as age, CT density (HU), and initial size, were dichotomized at clinically appropriate cutoff values (60 years, −500 HU and 10 mm, respectively). In the second study, a logistic-regression analysis was performed to clarify variables that affected GGO growth incidence. Finally, variables were selected by multivariate matched sampling methods in both studies.

RESULTS

Characteristics of GGOs with Growth

The clinical and radiologic characteristics of all cases were presented in Table 1. Among 125 patients with GGOs who underwent repeated TSCT for 3 months or more, 26 patients (21%) had overt GGO growth which met our definitions. With 13 GGOs (10%), enlargement of the greatest dimension was documented. These lesions consisted of 8 GGOs of 5 to 13 mm and 5 part-solid GGOs of 8 to 16 mm, and 2 of each had a history of lung cancer. An increase in both the greatest dimension and the size of the solid part was evident in 7 part-solid GGOs (6%) of 11 to 17 mm. Six GGOs measuring 8 to 16 mm became part-solid GGOs (5%).

The histopathological features were studied in 9 GGOs with growth. Specimens were obtained by surgical exploration in 7 (5 with lobectomy and 2 with segmentectomy), and by fine needle aspiration and by transbronchial lung biopsy in one each. The histologic diagnosis was made according to the World Health Organization classification[11]: adenocarcinoma with mixed subtype was seen in 6, nonmucinous BAC in 2, and organizing pneumonia in one. Of these 9 GGOs that underwent evaluation, 6 were detected at a health check-up and the rest were detected more than 2 years after an operation for stage I lung cancer. In contrast, 9 of the remaining 17 cases with growing GGOs had advanced tumors. Further evaluation was applied mainly depending on the background and the patient's request, particularly in the earlier period because the natural history of GGO had not yet been well described. No metastasis or tumor-related deaths were observed clinically.

Time to GGO Growth Curves and Univariate Analysis for Factors that Affect the Time to GGO Growth

The time to GGO growth curve for 125 GGOs is shown in Figure 3. Growth incidence at 3 and 5 years were estimated

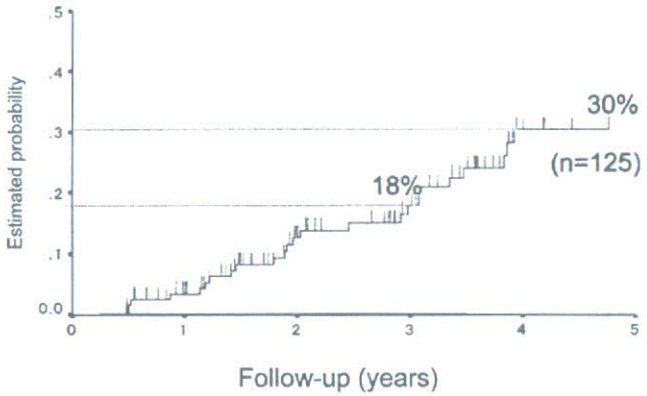

FIGURE 3. The time to GGO growth curve for the 125 GGOs. The growth incidence at 5 years was estimated to be 30% in this study.

TABLE 2. Univariate Analysis for Factors Affecting the Time to GGO Growth

Variables	Estimated Probability 3 yr	5 yr	p
Gender			0.15
Men	0.26	0.39	
Women	0.13	0.25	
Age			0.017
≤60	0.09	0.13	
60<	0.23	0.41	
Smoking habit			0.16
Never	0.09	0.23	
Ever	0.29	0.41	
History of lung cancer			0.22
With	0.19	0.22	
Without	0.16	0.38	
Initial size			<0.01
≤10	0.04	0.14	
10<	0.49	0.66	
Existence of solid part			<0.01
Without (GGO)	0.12	0.18	
With (part-solid GGO)	0.43	0.80	
CT density (HU)			0.17
≤−500	0.16	0.20	
−500<	0.20	0.40	
Location[a]			0.78
Above	0•19	0.31	
Below	0.13	0.28	
Multiplicity			0.60
Solitary	0.22	0.35	
Multiple	0.10	0.23	

[a] With reference to the major fissure of the lung.
GGO, ground-glass opacity; CT, computed tomography.

to be 18% and 30%, respectively, with no plateau. Statistically significant influence on time to growth was evident for age ($p = 0.017$), existence of solid part ($p < 0.01$) and initial size ($p < 0.01$). With regard to the initial size of GGO, we determined an appropriate cutoff size by using the time to GGO growth curve and found that 2 curves were maximally distinguished with an initial size of 10 mm. However, no differences in the time to GGO growth were observed according to such clinical factors as gender, smoking habit, history of lung cancer, or radiologic findings like size, existence of solid part, CT density, location, or multiplicity (Table 2). The time to GGO growth curves with reference to initial sizes (10 mm or smaller and larger than 10 mm) are shown in Figure 4 and the growth incidence of each group at 5 years were estimated to be 14% and 66%, respectively, the difference being statistically significant ($p < 0.01$).

Multivariate Analyses for Factors that Affect GGO Growth

The results of the multivariate analysis by Cox's proportional hazard model are shown in Table 3. Only initial size was significantly associated with the time to GGO growth ($p < 0.01$). In contrast, both the initial size ($p = 0.018$) and

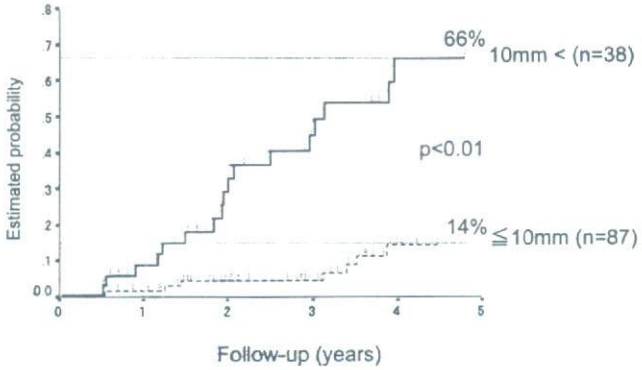

FIGURE 4. The time to GGO growth curves according to initial size of GGO. The growth incidence for 10 mm or smaller ($n = 87$) and larger ($n = 38$) at 5 years were 14% and 66%, respectively. The difference between the curves was statistically significant ($p < 0.01$).

TABLE 3. Multivariate Analysis for Factors Affecting the Time to GGO Growth by Cox Proportional Hazard Model

	SD	HR	95% CI	p
Gender	0.55	0.71	0.24–2.11	0.54
Age	0.028	1.00	0.95–1.06	0.79
History of lung cancer	0.61	2.15	0.65–7.15	0.21
Smoking habit	0.60	1.54	0.47–5.12	0.68
Initial size	0.085	1.28	1.08–1.51	<0.01
Existence of solid part	0.76	1.66	0.37–7.37	0.51
CT density (HU)	0.002	1.00	0.99–1.00	0.89
Location	0.56	0.86	0.29–2.57	0.79
Multiplicity	0.55	0.63	0.21–1.85	0.40
Final model				
Initial size	0.06	1.36	1.21–1.53	<0.01

GGO, ground-glass opacity; SD, standard deviation; HR, hazard ratio; CI, confident interval.

TABLE 4. Multivariate Analysis for Factors Affecting the Time to GGO Growth by Logistic Regression

	SD	OR	95% CI	p
Gender	0.78	0.47	0.10–2.16	0.33
Age	0.035	0.99	0.93–1.07	0.95
History of lung cancer	0.74	4.80	1.13–20.33	0.033
Smoking habit	0.76	0.91	0.21–4.03	0.91
Initial size	0.11	1.29	1.05–1.60	0.018
Existence of solid part	0.80	1.84	0.39–8.75	0.44
CT density (HU)	0.002	1.00	0.99–1.005	0.70
Location	0.67	0.62	0.17–2.29	0.47
Multiplicity	0.69	0.53	0.14–2.05	0.36
Final model				
Initial size	0.080	1.42	1.21–1.66	<0.01
History of lung cancer	0.53	3.51	1.25–9.88	0.017

GGO, ground-glass opacity; SD, standard deviation; OR, odds ratio; CI, confident interval.

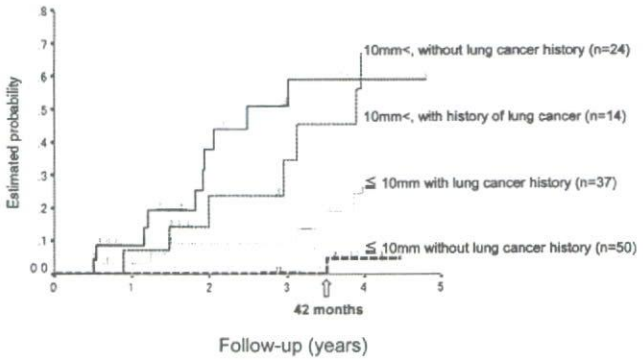

FIGURE 5. The time to GGO growth curve was divided according to the initial size and a history of lung cancer. Fifty GGOs that were 10 mm or less in diameter and without a previous history of lung cancer did not grow within the follow-up period of 42 months.

history of lung cancer ($p = 0.033$) were independent factors that were significantly associated with GGO growth on multivariate analysis of logistic regression (Table 4). The factor "history of lung cancer" seemed to influence the growth incidence after the third year of follow-up and this might be the reason why this parameter became significant only when using the logistic regression model. The time to GGO growth curves according to the initial size and history of lung cancer were shown in Figure 5. The growth population of 50 GGOs that were 10 mm or smaller and without a history of lung cancer stayed 0% until 42 months. However, the growth population of other GGOs started to rise within the first year.

DISCUSSION

Localized GGOs found on high-resolution chest CT scans have been reported to correspond histologically to preinvasive or early stage forms of adenocarcinoma.[6–11] Although the natural history of GGOs is speculated to correspond to progression from AAH to invasive adenocarcinoma, sequential changes are not well detailed. Clinically, localized GGOs are considered to exhibit slow growth.[12] Hasegawa et al. showed that the tumor doubling times of GGOs and solid-type lesions were 813 ± 375 and 149 ± 125 days, respectively.[13] Since biopsy or excision of these lesions in the lung is relatively difficult, these slow growing GGOs are currently considered for follow-up instead of definite diagnosis or treatment.[16,17] However, an appropriate follow-up period and a consensus intervention strategy have yet to be determined.

Recently, a close correlation between the size of resected GGOs and histology was reported. Nakata et al. analyzed GGOs less than 2 cm in diameter and found that the average sizes for AAH, BAC, and adenocarcinoma were 6.8 mm, 10.0, and 12.5 mm, respectively; the difference being statistically significant.[7] According to Takashima et al. lesion size, percentage of GGO area within a lesion, lobulation, coarse spiculation, air bronchogram, cavity, a pleural tag, and a solid portion are related to histopathological diagnosis as AAH, BAC, or adenocarcinoma.[18] Furthermore, the growth fraction of these tumor cells is known to increase according to sequential progression from AAH to BAC then adenocarcinoma.[19] These observations suggested that larger GGOs are more likely to have an invasive character, and therefore a high growth incidence can reasonably be expected for larger GGOs. In the present study, 26 of 125 GGOs (21%) showed obvious growth during the follow-up period, and the initial size of GGO was identified as an independent factor that affected GGO growth incidence and the time to GGO growth on multivariate analyses. In the International Early Lung Cancer Action Project protocol, observation and follow-up CT scan within a few months is recommended for any GGO 8 to 15 mm in diameter.[16] In the present study, the difference in growth population curves for GGOs 10 mm or smaller and GGOs larger than 10 mm was statistically significant. Therefore the interval of follow-up TSCT for each case should be set differently according to the initial size.

Moreover, our multivariate analysis demonstrated that a past history of lung cancer was also an independent factor affecting the growth of GGO. Kodama et al. reported similar observations; 19 GGOs were followed up, and growth was seen in 6 of 7 GGOs with a history of lung cancer but in only 4 of 12 GGOs without such a history.[20] Although the reason for the higher growth incidence in patients with a history of lung cancer is unclear, one possibility is that these newly developing GGOs are intrapulmonary metastases or recurrences. However, none of our 51 patients with a past history of lung cancer developed extrathoracic metastasis or bilateral multiple metastasis during the follow-up period. Therefore, the significant percentage in the present series can not be explained on this basis. Also, in CT images, recurrent intrapulmonary metastases are not likely to present with a GGO appearance.[5,21] Another possibility is that these GGOs are metachronous second primary lesions with a more aggressive nature and a faster speed of growth. In previous reports, the prevalence of second primary lung cancers was reported to be 0.8 to 10.0%, and the 5-year survival rate after the development of metachronous lesion varied from 18 to 39%.[22–26]

However, these reports considered only solid tumors of different histologies and of larger size than recent CT detected tumors, so much better survival is expected for GGOs even with a prior history of lung cancer. Without genetic confirmation, it is difficult to distinguish between metastasis or recurrence and second primary tumor, even with a comparison of histology.[27,28] In the present study, however, it was strongly suggested that the GGOs need to be carefully followed-up in patients with a history of lung cancer.

The timing of terminating the follow-up is another important issue in the management of GGO. In the present study, 50 GGOs that were 10 mm or less in diameter and without a previous history of lung cancer did not grow within the follow-up period of 42 months. Although the number of patients studied here was not large, these data suggested that the interval between the initial CT and the second CT for such GGOs could be extended to at least 3 years. Further accumulation of data is crucial to establish an appropriate follow-up strategy for patients with GGO lesions with varied backgrounds.

In conclusion, independent factors that significantly affect the growth of GGO were initial size, in particular larger than 10 mm, and a history of lung cancer in our series. Therefore, in the follow-up/work-up strategy for GGOs, these two factors should be taken into consideration so as not to overlook aggressive tumors. It is also important to note that these recommendations should be applied only after initial management and a 3-month follow-up have been performed. The possibility of putting-off the follow-up CT for 3 years for a GGO of 10 mm or smaller in a patient without any history of lung cancer should also be explored. In contrast, follow-up CT within a year should be recommended for larger GGOs or GGOs with a history of lung cancer.

ACKNOWLEDGMENTS

We greatly appreciate the technical support of Mr. Tomomasa Terahira at the Cancer Institute Hospital, Tokyo, Japan and the assistance of Drs. Masato Matsushima and Mio Sakuma at the Division of Clinical Research and Development, The Jikei University School of Medicine, with the data analysis.

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Disease-Free Interval Length Correlates to Prognosis of Patients Who Underwent Metastasectomy for Esophageal Lung Metastases

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Background: Pulmonary metastasectomy is a standard method for treatment of selected pulmonary metastases cases. Nevertheless, because prognosis for patients with lung metastases from esophageal cancer who have undergone pulmonary metastasectomy is poor, candidates for this method of treatment are rare. Therefore, the efficacy of surgical treatment for pulmonary metastatic lesions from esophageal cancer has not been thoroughly examined.

Methods: Between March 1984 and May 2006, 57 patients underwent resection of pulmonary metastases from primary esophageal cancer. These cases were registered in the database developed by the Metastatic Lung Tumor Study Group of Japan and were retrospectively reviewed from the registry. After excluding eight cases because of missing information, we reviewed the remaining 49 cases and examined the prognostic factors for pulmonary metastasectomy for metastases from esophageal cancer.

Results: There were no perioperative deaths. After pulmonary metastasectomy, disease recurred in 16 (33%) of the 49 patients. The overall 5-year survival was 29.6%. Median survival time was 18 months. The survival of patients with a disease-free interval (DFI) less than 12 months was significantly lower than patients with a DFI greater than 12 months. Through multivariate analysis, we identified DFI as a clinical factor significantly related to overall survival ($p = 0.04$).

Conclusions: We identified that patients with a DFI less than 12 months who underwent pulmonary metastasectomy for metastases from esophageal cancer had a worse prognosis. Pulmonary metastasectomy for esophageal cancer should be considered for selected patients with a DFI ≥12 months.

Key Words: Esophageal cancer, Pulmonary metastasis, Metastasectomy.

(*J Thorac Oncol.* 2008;3: 1046–1049)

Pulmonary metastasectomy is a standard method of treatment for selected pulmonary metastases cases.[1] When patients are appropriately selected for this treatment, the overall 5-year survival after pulmonary metastasectomy is about 30 to 40%.[1,2] In general, because prognosis for patients who have undergone this method of treatment is poor with disease frequently recurring, pulmonary metastasectomy is not a frequently chosen method of treatment for lung metastases from esophageal cancer. Consequently, survival after surgery for pulmonary metastases from esophageal cancer has not been thoroughly examined. In Japan, the annual report by the Japanese Association for Thoracic Surgery does not document patients who underwent metastasectomy for metastasized esophageal cancer.[3] Because the outcome of pulmonary metastasectomy for metastases from esophageal cancer has not been thoroughly investigated, it is controversial whether surgery is an effective treatment for metastatic esophageal cancer. To identify prognostic factors of pulmonary metastasectomy for metastases from esophageal cancer, in the present study, we reviewed cases registered in the Metastatic Lung Tumor Study Group of Japan database of patients who underwent metastasectomy for metastasized esophageal cancer.

PATIENTS AND METHODS

The Metastatic Lung Tumor Study Group of Japan developed a database for registration of lung metastases cases. These patients all underwent surgical resection. The database documents the following parameters: gender; age; histology; status of the primary tumor; treatment for the primary tumor; date of primary surgery; kind of surgery; curability; date of metastasis; disease-free interval (DFI); side, size and numbers of resected metastases; date of metas-

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/08/0309-1046

tasectomy; and follow-up. Between March 1984 and May 2006, 57 patients underwent resection of pulmonary metastases from primary esophageal cancer. These cases were registered in the Metastatic Lung Tumor Study Group of Japan database and were retrospectively reviewed from the registry. Preoperative examination, surgical indication, and operative procedure were at the discretion of each institution.

After excluding eight cases because of missing information such as number of resected metastases, age, or DFI, we examined the remaining 49 cases (46 males and 3 females) in our study. Surgery alone for the primary tumor was performed in 26 cases (53%), surgery and chemoradiotherapy were performed in 7 cases (14%), surgery and radiotherapy were performed in 6 cases (12%), surgery and chemotherapy were performed in 3 cases (6%), radiotherapy alone was performed in 2 cases (4%), and treatment data were not available for 5 cases (10%). We examined the following variables (Table 1): age (≥70 or <70), number of resected metastases (solitary or multiple), resected side (unilateral or bilateral), tumor size (≥3 or <3cm), DFI (≥12 or <12 months), surgical procedure (partial resection, segmentectomy, or lobectomy), and curability (complete or incomplete).

The present study was analyzed using anonymized data that were collected in each institution. Therefore, informed consent was not specifically obtained and institutional review board approval was not necessary.

Statistical Analysis

Overall survival was analyzed by the Kaplan-Meier method, and differences in variables were calculated by the log-rank test. The date of pulmonary resection was defined as the starting point. Cox's proportional hazards model was used for multivariate analysis. The data were calculated using version 5.0 of the StatView software package (SAS Institute Inc, Cary, NC). A p value of less than 0.05 was defined as indicative of statistical significance.

TABLE 1. Survival of 49 Patients According to Clinical Factors of Pulmonary Metastases

Variables	n (%)	5-yr Survival (%)	p
Age (yr)			
≥70	13 (27)	32.9	0.928
<70	36 (73)	27.8	
Number			
Solitary	39 (80)	27.4	0.797
Multiple	10 (20)	42.9	
Resected side			
Unilateral	44 (90)	29.3	0.621
Bilateral	5 (10)	30.0	
Tumor size[a]			
≥3 cm	10 (21)	40.0	0.640
<3 cm	38 (79)	26.7	
DFI			
≥12 mo	28 (57)	39.2	0.048
<12 mo	21 (43)	15.7	
Surgical procedure			
Partial and segment	31 (63)	36.4	0.338
Lobectomy	18 (37)	22.9	
Curability			
Complete	45 (92)	31.4	0.990
Incomplete	4 (8)	25.0	

[a] No cases were available.
DFI, disease-free interval.

RESULTS

The median interval between treatment of esophageal cancer and diagnosis of pulmonary metastasis (disease-free interval) was 14 months (range: 0–124 months). There were no perioperative deaths. The median age of patients at the time of pulmonary metastasectomy was 65 years (range: 35–82). The median number of resected metastatic lesions per patient was one (range: 1–5). The metastases ranged in size from 0.4 to 5.5 cm, and the median size was 2.0 cm. The metastases were squamous cell carcinoma in 48 cases and adenocarcinoma in one case. The surgical procedure was wedge resection in 23 cases (47%), lobectomy in 16 cases (33%), segmentectomy in 8 cases (16%), and bilobectomy in 2 cases (4%). The median follow-up period after the first pulmonary resection was 18 months (range: 0–206 months). Recurrence developed in 16 (33%) of the 49 patients. Recurrences were as follows: lung, nine; lymph node, three; neck, one; distant metastasis, one; stomach, one; and unknown, two. The overall 5-year survival after pulmonary metastasectomy was 29.6% (Figure 1). Median survival time was 27 months. We investigated the relationships between prognostic factors and survival (Table 1). Patients with a DFI less than 12 months had a significantly worse prognosis, as assessed by survival rates, than patients with a DFI greater than 12 months (Figure 2). Multivariate analysis of these variables was performed using Cox's proportional hazards model for disease-specific survival. A DFI less than 12 months was shown to be an independent prognostic factor ($p = 0.04$) (Table 2). At the time of submission, 28 patients examined in our study have died Although 23 patients died of esophageal cancer, 7 patients were not available for recurrent sites. Five patients have died of other diseases (two cases

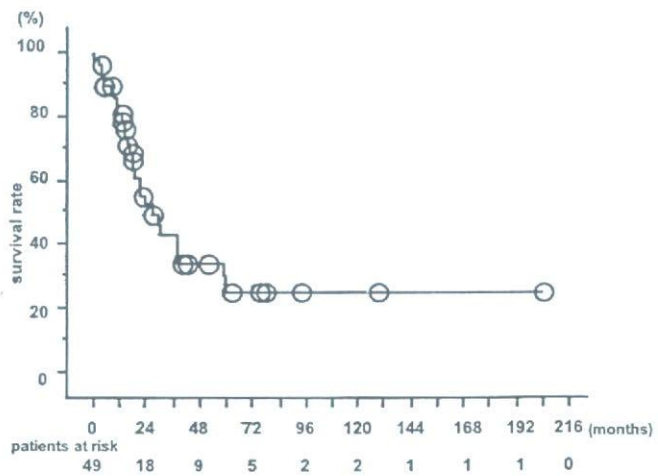

FIGURE 1. Overall survival of the 49 patients after pulmonary metastasectomy. The 5-year survival was 29.6%.

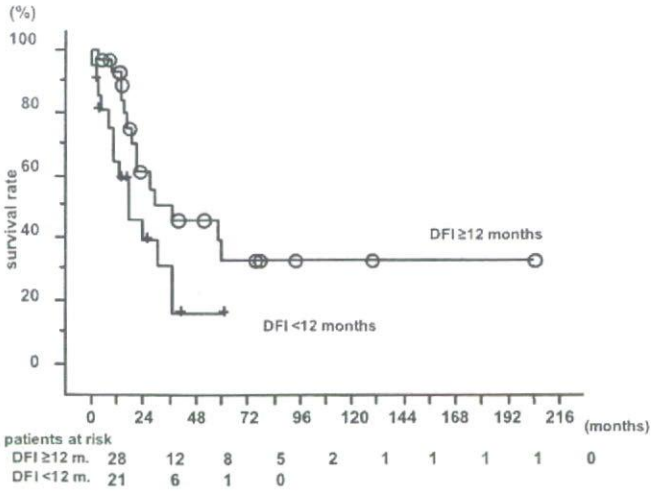

FIGURE 2. Overall survival after pulmonary metastasectomy according to DFI. Survival curves of patients with DFI <12 months and ≥12 months. DFI, disease-free interval.

TABLE 2. Relationships of Individual Variables to Survival (Cox's Proportional Hazards Model)

Variable	Risk Ratio	95% CI	*p*
≥70 yr	1.01	0.41–2.50	0.983
Multiple metastasis	1.67	0.30–9.19	0.557
Bilateral metastasis	1.19	0.19–7.53	0.853
Tumor size ≥3 cm	0.76	0.25–2.35	0.635
DFI <12 mo	2.30	1.04–5.09	0.040
Partial and segment	0.60	0.22–1.65	0.180
Incomplete resection	1.00	0.22–4.56	0.881

CI, confidence interval; DFI, disease-free interval.

were pneumonia, two cases were cerebral infarction, and one case was myocardial infarction).

DISCUSSION

Patients who are candidates for pulmonary metastasectomy for metastases from esophageal cancer are a minority. Analysis of the outcomes of surgery for pulmonary metastases from esophageal cancer has not been published. Quint et al.[4] showed that 29 of 147 (20%) patients with newly diagnosed metastasized esophageal cancer had lung metastasis. Although autopsy studies showed that the frequency of esophageal lung metastasis was 50%,[5] there was not a high percentage of esophageal cancer relapse after esophagectomy. Kyriazanos et al.[6] revealed that 12 of 151 (8%) patients who underwent a curative esophageal resection had lung metastases. Within our study the number of adenocarcinoma of the esophagus was very small. Because the frequency of adenocarcinoma of the esophagus is low in Japan, we do not speculate about the scarce incidence of lung metastasis from adenocarcinoma of the esophagus.

Matsubara et al. showed that 38 of 230 patients (17%) who underwent surgery for esophageal cancer with extended lymph node dissection had distant metastases and 14 (6%) patients had lung metastases. In their article, the outcomes after recurrence were dismal, and no patients were alive 5 years after detection of recurrence. Nevertheless, they showed that the 1-year survival of the patients who had recurrent lesions and were treated with resection and adjuvant therapy was 83%. They concluded that when recurrent lesions were localized macroscopically, surgical removal of the recurrent lesions was an effective treatment.[7] Through our analysis, we found a 5-year survival of 29.6% after pulmonary metastasectomy, which indicates that pulmonary metastasectomy is a promising treatment for metastases from esophageal cancer. Nevertheless, as it is not easy to differentiate esophageal metastases from primary lung squamous cell carcinomas, it is possible that our data might include primary lung squamous cell carcinoma. Survival after metastasectomy might be lower than what our data indicate. Virgo et al mentioned that genetic markers are needed to confidently distinguish between metastases and primary solitary nodules.[8] Further investigation is needed to clarify this matter.

An article from the international registry of lung metastases states that the 5-year survival was 37% after pulmonary metastasectomy. In addition, the article showed that among cases of complete resection, the 5-year survival was 33% for patients with a DFI of 0 to 11 months and 45% for those with a DFI of more than 36 months. Furthermore, the 5-year survival was 43% for single lesions and 27% for 4 or more lesions.[1] DFI and number of pulmonary metastases are significant prognostic factors. Because our present data show that the median DFI is 14 months, we categorized DFI as ≥12 or <12 months. Regarding the DFI, our study suggests that patients with a DFI less than 12 months have a poor prognosis. Osugi et al. showed that 83% of recurrences presented within 24 months after esophagectomy and that the chance of survival of patients whose disease recurred within 24 months after esophagectomy was better than that of patients who suffered recurrence within 24 months. Regarding follow-up studies after esophagectomy, meticulous care should be taken to detect hematogenous recurrence.[9]

In general, incomplete resection is a dismal prognostic factor in lung metastasectomy. We could not demonstrate whether surgical curability is a prognostic factor. McDonald et al. reported that incomplete resection appeared to have no influence on overall survival in metastatic breast cancer. They suggested that this could be due to the systemic nature of the disease at the time of thoracotomy with unsuspected occult metastasis in other areas.[10] Nevertheless, in our study, only four patients underwent incomplete resection. Because the report from The International Registry of Lung Metastases stated that cases with incomplete resection clearly had worse prognoses,[1] we speculate that patients with lung metastases from esophageal cancer have the same tendency.

Although our present study was multi-institutional, we could not analyze in detail all of the records for each patient. From this point of view, because our findings were based on a limited number of cases, pulmonary metastasectomy for lung metastases from esophageal cancer is still highly controversial. Nevertheless, we identified that patients with a DFI less than 12 months had a worse prognosis, as assessed by

survival rates, than patients with a DFI greater than 12 months.

Consequently, although metastases from esophageal cancer are a minority, we think that pulmonary metastasectomy for esophageal cancer should be considered for selected patients with a DFI ≥12 months. As this study is small, further clinical studies will be needed.

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VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Preoperative Chemoradiotherapy Followed by Surgical Resection in Patients With Superior Sulcus Non–Small-Cell Lung Cancers: Report of Japan Clinical Oncology Group Trial 9806

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Submitted September 1, 2007; accepted October 25, 2007.

Supported by the Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (Grants No. 11S-2, 11S-4, 14S-2, 14S-4, 17S-2, and 17S-5).

Presented in part at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31-June 3, 2003, Chicago, IL, and at the 11th World Conference on Lung Cancer, July 3-6, 2005, Barcelona, Spain.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2604-644/$20.00

DOI: 10.1200/JCO.2007.14.1911

ABSTRACT

Purpose
To evaluate the safety and efficacy of preoperative chemoradiotherapy followed by surgical resection for superior sulcus tumors (SSTs).

Patients and Methods
Patients with pathologically documented non–small-cell lung cancer with invasion of the first rib or more superior chest wall were enrolled as eligible; those with distant metastasis, pleural dissemination, and/or mediastinal node involvement were excluded. Patients received two cycles of chemotherapy every 4 weeks as follows; mitomycin 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, and cisplatin 80 mg/m^2 on day 1. Radiotherapy directed at the tumor and the ipsilateral supraclavicular nodes was started on day 2 of each course, at the total dose of 45 Gy in 25 fractions, with a 1-week split. Thoracotomy was undertaken 2 to 4 weeks after completion of the chemoradiotherapy. Those with unresectable disease received boost radiotherapy.

Results
From May 1999 to November 2002, 76 patients were enrolled, of whom 20 had T4 disease; 75 patients were fully assessable. Chemoradiotherapy was generally well tolerated. Fifty-seven patients (76%) underwent surgical resection, and pathologic complete resection was achieved in 51 patients (68%). There were 12 patients with pathologic complete response. Major postoperative morbidity, including chylothorax, empyema, pneumonitis, adult respiratory distress syndrome, and bleeding, was observed in eight patients. There were three treatment-related deaths, including two deaths owing to postsurgical complications and one death owing to sepsis during chemoradiotherapy. The disease-free and overall survival rates at 3 years were 49% and 61%, respectively; at 5 years, they were 45% and 56%, respectively.

Conclusion
This trimodality approach is safe and effective for the treatment of patients with SSTs.

J Clin Oncol 26:644-649. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Superior sulcus tumors (SSTs), involving structures at the thoracic inlet, represent a small subtype of non–small-cell lung carcinoma (NSCLC). These SSTs, first described by Henry Pancoast[1,2] and thus also called Pancoast tumors, have posed a challenging problem for surgeons, radiation oncologists, and medical oncologists alike, ever since they were first described.[3]

Preoperative radiotherapy has long been the community standard in the management of SSTs.[4-17] However, both the complete resection rate (approximately 50%) and long-term survival rate (approximately 30%) have remained poor and unchanged over the last 40 years, since the first treatment strategy was reported in the 1960s. Local control has remained the main problem,[15,17,18] adversely affecting quality of life as well as survival of patients. Presence of mediastinal lymph node metastasis (N2 status) has been reported to be associated with a particularly poor prognosis.[9,18]

However, a series of clinical trials over the last two decades have shown concurrent chemoradiotherapy to be beneficial in the treatment of unresectable stage III NSCLC.[19-21] The addition of chemotherapy to thoracic radiotherapy seems to suppress distant micrometastases,[22,23] and giving

concurrent chemotherapy with radiotherapy has been shown to yield improved local control[19,24] with survival benefit.

Encouraged by the promising data of concurrent chemoradiotherapy for N2 NSCLC, the Southwest Oncology Group (SWOG) applied this modality as preoperative therapy for patients with SSTs (SWOG 9416, Intergroup Trial 0160), and reported favorable results.[25]

The Japan Clinical Oncology Group (JCOG) launched another trial of this preoperative concurrent chemoradiotherapy, or the trimodality approach, for the treatment of SSTs in 1999, before the first report of SWOG 9416 was published. Our study was initiated to evaluate the safety and efficacy of this treatment strategy in this rare subset of patients with NSCLC. As the induction treatment, we used mitomycin, vindesine, and cisplatin (MVP) combination chemotherapy, which has been demonstrated to be safe and effective for concurrent chemotherapy with thoracic radiotherapy in Japanese trials.[19]

Eligibility Criteria

Patients with untreated histologically or cytologically documented NSCLC involving the superior sulcus with clinical stage T3 or T4 disease were eligible for entry onto this study. T4 diseases included tumor invasion to the spine (including to a transverse process of vertebra), aorta, or superior vena cava; invasion to the chest wall or subclavian vessels was included in T3 disease. Involvement of the superior sulcus was confirmed by computed tomographic (CT) or magnetic resonance imaging (MRI) evidence of tumor invasion of the first rib or more superior chest wall. Patients with pleural or pericardial dissemination, malignant effusion, and/or distant metastasis (M1) were excluded. Those with clinical N2 disease (mediastinal node involvement) were also excluded; all mediastinal nodes measuring ≥ 1.0 cm in size on CT images were required to be biopsied and documented to be negative for metastasis before patient enrollment. However, those with ipsilateral supraclavicular node involvement (N3) were eligible, unless it was accompanied by mediastinal node metastasis. Each patient was required to fulfill the following criteria: 15 to 74 years of age, Eastern Cooperative Oncology Group performance status of 0 to 1; adequate organ function (ie, leukocyte count ≥ 4,000/μL, platelet count ≥ $10^5/\mu$L, hemoglobin ≥ 11.0 g/dL, serum creatinine less than 1.5 mg/dL, creatinine clearance ≥ 60 mL/min, serum bilirubin less than 1.5 mg/dL, serum ALT and AST less than double the upper limit of the institutional normal range, arterial partial pressure of oxygen ≥ 70 mmHg, and predicted postoperative forced expiratory volume in 1 second ≥ 0.8 L. From July 2001, when the protocol was revised after the death of a patient from septic shock during chemoradiotherapy, those patients with systemic use of corticosteroids were excluded.

Patient eligibility was confirmed by the JCOG Data Center before patient registration. This study was approved by the institutional review boards at each participating center, and written informed consent was obtained from all patients.

Treatment Plan

Induction chemotherapy. Patients received two courses of MVP combination chemotherapy with a 4-week interval in between. Mitomycin was administered at 8 mg/m^2 on chemotherapy day 1, and vindesine was administered at 3 mg/m^2 on days 1 and 8; both were administered as bolus injections. Cisplatin was administered at 80 mg/m^2 as a 2-hour infusion on day 1, with ample hydration and antiemetic administration.

The second cycle of chemotherapy was postponed until all the severe toxicities recovered to grade 1 or 0. If the second cycle could not be started within 2 weeks of the due date, it was canceled, and the patient received only preoperative radiotherapy, if possible.

Induction radiotherapy. Thoracic radiotherapy was started with a linear accelerator (≥ 4 MeV) on chemotherapy day 2. The first session was scheduled to be given with the first chemotherapy cycle at 27 Gy in 15 fractions over 3 weeks. Then the second session was started after a week's interval until day 2 of the second course of chemotherapy. The second session, given with the second cycle of MVP, was administered at 18 Gy in 10 fractions over 2 weeks. The total radiation dose was thus 45 Gy in 25 fractions administered over 6 weeks, including the 1-week split, or interval, between the two sessions; this schedule, including the split, basically followed that of the original method reported by Furuse et al.[19] The radiation field included the primary tumor and the ipsilateral supraclavicular nodes. The mediastinal and hilar nodes were not irradiated, even in cases with hilar node involvement (clinical N1 cases).

Surgery. After the induction chemoradiotherapy, each case was re-evaluated to determine the clinical response and resectability. The resectability of the tumor was determined by the multimodality team of each institution, irrespective of the clinical response (tumor shrinkage). Surgical resection of the tumor was performed 2 to 4 weeks after the completion of the induction therapy. The surgical procedures undertaken included lobectomy or pneumonectomy, with systematic node dissection. Standard systematic node dissection, ND2, includes complete removal of the hilar and mediastinal nodes. Less complete dissection includes ND0 (ie, no systematic dissection with or without lymph node sampling) or ND1 (ie, hilar node dissection with or without mediastinal lymph node sampling).

Boost therapy. For unresected or incompletely resected cases, boost radiotherapy of 21.6 Gy in 12 fractions was given. Those who were judged to have undergone complete resection were followed up without additional therapy until clinical evidence of recurrence.

Patient Evaluation and Follow-Up

Before enrollment onto the study, each patient underwent complete medical history taking and physical examination, blood cell count determinations, serum biochemistry testing, arterial blood gas analysis, chest x-ray, ECG, CT scan of the chest, bronchoscopy, CT scan or ultrasound of the upper abdomen, whole-brain CT or MRI, and an isotope bone scan. Chest MRI was recommended for evaluation of the local tumor status but was not mandatory. Blood cell counts, serum biochemistry testing, and chest x-ray were performed weekly during each course of chemotherapy. Chest CT was performed every 3 to 4 weeks during the induction therapy.

Chemotherapy toxicity was evaluated according to the JCOG Toxicity Criteria,[26] modified from the National Cancer Institute Common Toxicity Criteria version 1. Tumor responses were assessed radiographically according to the standard, two-dimensional WHO criteria[27] and were classified into complete response (CR), partial response, no change, progressive disease (PD), and not assessable. Response confirmation at 4 weeks or longer intervals was not necessitated. After curative resection and/or definitive boost radiotherapy, the patients were followed up with periodic re-evaluation, including with chest CT, as well as a systemic survey every 6 months for the first 3 years.

Central Review

Radiographic reviews for eligibility of the enrolled patients and the clinical responses were performed at the time of the JCOG Lung Cancer Surgical Study Group meeting, held every 3 to 4 months. The study coordinator (H.K., a medical oncologist), the group coordinator (M.T., a surgical oncologist), and a few selected investigators of the group reviewed the radiographic films. The clinical response data presented below were all confirmed by this central review.

Statistical Considerations

The primary end point of the study was the survival rate at 3 years. The sample size calculation was performed, as described in Appendix 1 (online only).

Secondary end points included the objective tumor response to chemotherapy, complete resection rate, and postsurgical morbidity/mortality. Both overall survival (OS) and progression-free survival (PFS) were calculated from the date of enrollment by the Kaplan-Meier method. For exploratory analysis to identify prognostic factors, the OS or PFS of subgroups was compared by two-sided log-rank tests. All analyses were performed with the SAS software version 8.2 (SAS Institute, Cary, NC).

Patient Characteristics

From May 1999 to November 2002, 76 patients from 19 institutions were enrolled onto the study. Three patients were ineligible. One patient was found to have concomitant anemia and did not receive the protocol treatment. Two others were found ineligible by the central review, after completion of the protocol therapy; the tumor was judged not to involve the first rib in one case, and in the other, a mediastinal node was judged to be enlarged on chest CT, without confirmation by mediastinoscopy. These two cases were included in the analysis. Therefore, 75 patients were analyzed to determine the toxicities, response rates, surgical and pathologic results, PFS, and OS. All 76 patients were included in the analysis of the patient characteristics, as shown in Table 1. In each of the T4 cases, the tumor was judged to have involved the spine. Nodal status was clinically determined and was pathologically confirmed in only a few cases.

Induction Therapy Delivery and Toxicity

The study schema with the actual numbers of patients receiving the protocol therapy is shown in Appendix Figure A1 (online only).

Table 1. Patient Characteristics (n = 76)

Characteristic	No. of Patients	%
Sex		
Male	67	88
Female	9	12
Age, years		
Median	57.5	
Range	34-74	
ECOG performance status		
0	30	39
1	46	61
Clinical T stage		
T3	56	74
T4	20	26
Clinical N stage		
N0	59	78
N1	9	12
N2*	1	1
N3	7	9
Smoking history		
No	4	5
Yes	72	95
Median smoking history	1.5 packs for 37 years	
Body weight loss within 6 months		
≤ 5%	61	80
5-10%	7	9
> 10%	5	7
Missing	3	4
Histology		
Adenocarcinoma	34	45
Squamous cell carcinoma	27	36
Others/unclassified	15	20
Primary site		
Right	39	51
Left	37	49

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Found ineligible by central review but included in the subsequent analyses.

The induction therapy could be completed in 71 (95%) of the 75 patients. The treatment was terminated in the remaining four patients after only one course of chemotherapy (owing to the development of adverse events in two cases, patient refusal in one case, and early toxicity-related death in one case).

Table 2 lists the major toxicities of the protocol therapy. They were mainly hematologic, and although more than 80% of the patients experienced neutropenia/leukopenia, they were generally transient and not complicated by infection/fever. Overall, toxicities were well tolerated. There was one toxic death on chemoradiotherapy day 6 as a result of severe myelosuppression and subsequent development of septic shock.

Clinical Response to the Induction Therapy

The clinical responses of the 75 eligible patients to induction therapy were judged radiologically and confirmed by the central review. The responses were as follows: CR, 0 patients; partial response, 46 patients; no change, 22 patients; PD, five patients; not assessable, two patients. The overall response rate was 61% (95% CI, 49% to 72%).

Surgical and Pathologic Results

Thoracotomy was performed in 57 (76%) of the 75 patients who received the induction therapy. The surgical procedures undertaken

Table 2. Major Toxicities of Induction Therapy (N = 75) and Postsurgical Complications

Toxicity or Complication	No. of Patients			% Grade 3/4
	Grade 1/2	Grade 3	Grade 4	
Acute toxicity*				
Leukopenia	1/11	37	26†	84
Neutropenia	3/9	26	36†	83
Anemia	19/47	5	0	7
Thrombocytopenia	14/12	9	2†	15
ALT	27/5	2	0	3
Creatinine	18/2	0	0	0
PaO_2	37/6	0	0	0
Emesis	32/25	2	— (not defined)	3
Diarrhea	7/5	1	0	1
Constipation	22/3	1	0	1
Esophagitis	22/9	0	0	0
Infection	10/9	6	1†	9
Neuropathy	8/0	0	— (not defined)	0
Skin toxicity	16/2	1	0	1
Fever	25/19	1	1	3
Postsurgical complications‡				
ARDS	0	1	1 (grade 5)	
Empyema	0	2	0	
Cylothorax	1	1	0	
Pneumonitis	0	1	0	
Late complications‡				
Pneumonitis	0	1	0	
Bleeding	0	0	1 (grade 5)	

Abbreviations: PaO_2, alveolar-arterial difference in partial pressure of oxygen; ARDS, adult respiratory distress syndrome.
*During induction therapy.
†Includes one patient with toxic death owing to septic shock.
‡Report of each complication was evaluated by National Cancer Institute Common Toxicity Criteria version 3.0.

were as follows: lobectomy, 53 patients; partial resection, three patients; exploratory thoracotomy, one patient; none of the cases required pneumonectomy. Combined resection of the chest wall was undertaken in 51 of the 57 patients. Complete mediastinal lymph node dissection (ND2) was performed in 42 patients, and the remaining 15 patients underwent less extensive dissection or sampling (ND0 or ND1).

The results of thoracotomy were as follows: gross residual tumor (R2 resection, including one with probe thoracotomy), three patients; microscopically residual tumor on pathologic review (R1 resection), three patients; complete surgical and pathologic resection (R0 resection), 51 patients. Pathologic downstaging of the tumor as compared with the clinical stage before induction therapy was achieved in 23 patients (40% of the patients who underwent surgery); this is an inherently inaccurate figure and should be interpreted as such, owing to the lack of pathologic confirmation of the c stage at presentation. Pathologic CR, with no residual viable tumor cells in the resected specimens, was achieved in 12 patients (16% of the 75 treated patients). Table 3 lists the surgical and pathologic results according to the initial clinical T factor.

The major postoperative morbidities included adult respiratory distress syndrome (ARDS) in two patients, empyema in two patients, chylothorax in two patients, and pneumonitis in two patients. One patient died of sudden major bleeding on postoperative day 24. The bleeding was identified at autopsy as being from an intercostal artery. Another patient died of ARDS after off-protocol pneumonectomy. The patient had been judged to have PD in response to the induction therapy as a result of emergence of intrapulmonary metastases. The attending surgeon and the patient agreed to salvage surgery, and the patient developed postoperative ARDS.

Thus the total number of toxic deaths was three, including one caused by septic shock during the induction, one by delayed postoperative bleeding, and one by the development of ARDS after off-protocol, salvage surgery.

Table 3. Surgical and Pathologic Results According to Initial Clinical T Stage

Characteristic	c-T3	c-T4
No. of patients	55	20
No surgery performed		
No.	7	11
%	13	55
Reason for no surgery		
Protocol violation	0	1
Toxic death	0	1
Adverse event	0	1
Progressive disease	2	2
Judged unresectable	0	3
Patient refusal	5	3
Surgical procedures		
Thoracotomy		
No.	48	9
%	87	45
Pneumonectomy	0	0
Lobectomy	45	8
Probe thoracotomy	1	0
Other	2	1
With combined resection	44	7
Rib	38	6
Parietal pleura	4	1
Vertebra	3	3
Major vessel	3	0
Clavicle	1	0
Completeness of resection		
R2 operation	2	1
R1 operation	3	0
R0 operation		
No.	43	8
%	78	40
Pathologic results		
Downstaging	18	5
Pathlogic complete response	9	3

Boost Therapy

Boost radiotherapy was given to 15 patients, including 12 of the 15 patients in whom thoracotomy was not performed after the completion of induction chemoradiotherapy. One patient received boost radiotherapy after grossly incomplete resection, and another received boost radiotherapy after gross complete resection with microscopically residual disease. In 12 of the 15 patients, boost radiotherapy was completed with a total dose of 66.6 Gy.

PFS and OS

Figures 1 and 2 show the PFS and OS curves, updated in November 2006. Forty-one patients were alive, with a median follow-up period of 68 months. The median PFS time was 28 months. The PFS rates at 3 and 5 years were 49% and 45%, respectively. The median OS has not yet been reached. The OS at 3 and 5 years were 61% and 56%, respectively. Subset analysis (Appendix Figs A2 through A5, online only) revealed that clinical T stage was a prognostic factor (Appendix Fig A2). Patients with clinical T3 disease had better outcome than those with clinical T4 disease (the survival rates at 3 and 5 years were 69% and 61%, respectively, versus 40% and 40%, respectively; log-rank $P = .031$). The clinical N stage and histologic type of the tumor did not significantly affect the OS (Appendix Figs A3 and A4) or PFS. As expected, the survival rate was good in patients in whom complete resection could be achieved, with a projected 5-year OS of 70% as compared with 24% in whom complete resection could not be

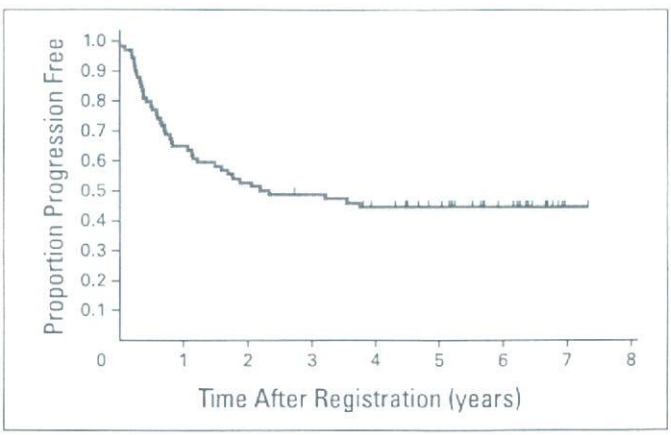

Fig 1. Progression-free survival (PFS) of the 75 eligible patients. PFS at 3 years and 5 years was 49% (95% CI, 38% to 60%) and 45% (95% CI, 34% to 56%), respectively, with a median PFS of 27.7 months.

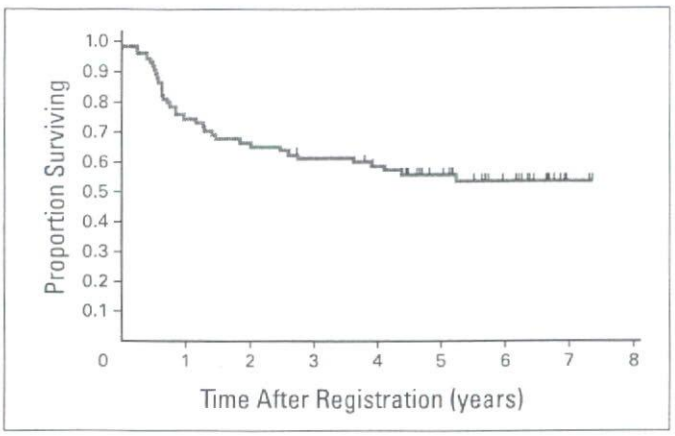

Fig 2. Overall survival (OS) of the 75 eligible patients. OS at 3 years and 5 years was 61% (95% CI, 49% to 71%) and 56% (95% CI, 44% to 66%), respectively. The median OS has not been reached.

achieved (Appendix Fig A5). The survival of the 12 patients with pathologic CR was especially favorable (Appendix Fig A6, online only).

Pattern of Relapse

So far, 39 patients have experienced tumor relapse. Table 4 lists the initial relapse sites, according to the curative extent of the surgical resection. For unresected or incompletely resected cases, locoregional relapse was predominant. To the contrary, for completely resected cases, relapse at distant sites was the most frequent relapse pattern, with some brain-only relapse patients.

DISCUSSION

We conducted a multi-institutional phase II trial of a trimodality approach, namely, preoperative chemoradiotherapy followed by surgical resection, in patients with SSTs. Because of the rarity of this subtype of NSCLC, no randomized trial has been conducted previously.[28] Our report is the second of a large-scale, prospective trial after SWOG 9416/INT 0160 and reproduced its favorable outcomes.[25]

The long-term results of the SWOG 9416/INT 0160 trial were recently published.[29] Although the chemotherapy regimens used were different, a standard classic platinum-based combination was used in both. The preoperative radiotherapy doses were also identical (45 Gy), although a 1-week split (interval between two sessions) was included in our protocol (but not in the SWOG trial). Boost chemotherapy was planned after curative resection in the SWOG trial, but the compliance rate was poor,[25] as in other perioperative therapy reports; we had anticipated that the majority of the patients would not be fit enough for additional toxic therapy after a major thoracic surgery and did not include it in our protocol.

Table 4. Initial Relapse Sites

Relapse Site	Patients With Complete Resection (n = 51)	Patients Without Complete Resection (n = 24)	Total (N = 75)
Locoregional* only	2	8	10
Distant only	14	6	20
Brain only	4	1	5
Both	4	5	9
Total	20	19	39

*Locoregional = surgical margin, within radiation field, hilar lymph nodes, mediastinal lymph nodes, supraclavicular lymph nodes.

Despite these minor differences, the results of the two trials were strikingly similar (Table A1, online only). The radiologic response rate was higher, whereas the pathologic CR rate was lower in our trial, but the differences were probably not clinically relevant, considering interobserver differences in the response evaluation and the well-known discrepancy between clinical versus pathologic effects. The intensive trimodality approach was found to be feasible in both reports, with a reasonably low toxic death rate of 4%. The resection rate, which had remained unchanged at approximately 50% for almost 40 years with conventional preoperative radiotherapy, was approximately 70% in both studies. Particularly noteworthy was the reproducibility of the favorable survival data, with a 5-year OS rate of 44% in the United States trial and 56% in our trial, which were clearly superior to the historical value of 30%.[3,25]

A shift in the trend of clinical problems also became clear.[25,28,29] The relapse patterns changed from predominantly locoregional[17,18] to mainly distant recurrences in cases with complete resection,[25,28,29] and a significant number of such patients suffered from metastasis in the brain as the initial site of relapse.[29] To the contrary, complete resection could be achieved in less than half of the patients with c-T4 disease, and neither local control nor long-term survival was satisfactory in those in whom it could not be achieved. It seems that there might be room for improvement in radiotherapy.

Several questions remain unresolved. One is that of management of patients with mediastinal node involvement. These clinical N2 cases have been known to have the poorest prognosis[9,18] and were excluded from both the SWOG and JCOG trials. Although trimodality approaches have been reported in cases with clinical N2 stage NSCLC,[30,31] inclusion of the hilar and mediastinal nodes in the irradiation field increased the toxicity risk to an unacceptable level in our prior phase II trial (JCOG 9805).[32]

In addition to the unresolved questions above, our study also had a critical limitation. Although this was a prospective, large-scale, and multi-institutional trial, no definite conclusions could be obtained from the single-arm phase II study. As repeatedly pointed out, however, a phase III trial would be unrealistic due to the rarity of SSTs. Possibly, clinical questions common with other patient subsets could be tested in a phase III trial targeting a broader patient population; for example, patients with SSTs and other stage III NSCLC could be enrolled onto a phase III trial of prophylactic cranial irradiation after definitive induction therapy.[33]

In conclusion, we report a favorable outcome of preoperative chemoradiotherapy in patients with SSTs, confirming the results of the previous SWOG/Intergroup trial. We believe that this strategy may be acceptable as standard for the treatment of this disease and also serves as a reference for future trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Acknowledgment

We thank Mieko Imai for data management and Takashi Asakawa and Naoki Ishizuka, PhD, for statistical analyses.

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 version (via Adobe® Reader®).

XVI. 特　　論

胃がん治療ガイドラインの患者・家族向け情報提供について

Information distribution of gastric cancer treatment guidelines to patients and their families

山口直人[1]　吉田雅博[2]　佐藤康仁[1]

Key words：胃癌，ガイドライン，患者

はじめに

胃癌は我が国で最も患者数の多いがんの一つであり，治療成績も海外よりも良好である．近年，診療ガイドラインの普及が進み，胃癌についても，胃癌学会が‘胃癌治療ガイドライン’を作成し出版している．胃癌学会は，患者・家族向けに，治療ガイドラインをわかりやすく解説した‘胃がん治療ガイドラインの解説’を出版している．

本稿では，両ガイドラインをインターネット上に掲載している日本医療機能評価機構の医療情報サービスMindsと，胃がん治療ガイドラインの解説を中心に，胃癌の一般向け情報提供について概説したい．

1. Mindsによる診療ガイドラインの情報提供

診療ガイドラインは，‘特定の臨床状況のもとで適切な判断を下せるよう医療者と患者双方を支援する目的で体系的に作成された文書’と定義されている．我が国では厚生省医療技術評価推進検討会が整備の推進を提言したことを受けて，国を挙げて診療ガイドラインを整備する研究事業が平成11年から本格化した．30疾患あまりの診療ガイドラインの作成が厚生労働科学研究費によって補助されており，その多くは既に完成している．また，学会などが独自に作成した診療ガイドラインは少なくとも100は既に完成しているといわれている．

我が国で診療ガイドラインの作成が軌道に乗りつつあることを受けて，厚生労働省では，完成した診療ガイドラインを普及させる事業にも力を入れることとなったが，これを担当することになったのが財団法人日本医療機能評価機構である．日本医療機能評価機構では平成14年度から厚生労働科学研究費の補助を受けて，EBMデータベース事業を開始し，通称名Minds（Medical Information Network Distribution Serviceの略）と呼ぶ医療情報サービスを提供することとなった．2年間の準備期間を経て平成16年5月からは一般公開が開始された．平成20年2月末現在で，医療提供者向けガイドラインとして，アルツハイマー型痴呆，胃潰瘍，胃癌，胃がん検診，潰瘍性大腸炎，肝癌，急性心筋梗塞，急性膵炎，急性胆管炎/胆嚢炎，クモ膜下出血，頸椎後縦靱帯骨化症，頸椎症性脊髄症，健康診査の健診項目，高血圧，骨粗鬆症，子宮体癌，周産期ドメスティック・バイオレンス，小児急性中耳炎，上腕骨外側上顆炎，褥瘡，膵癌，前

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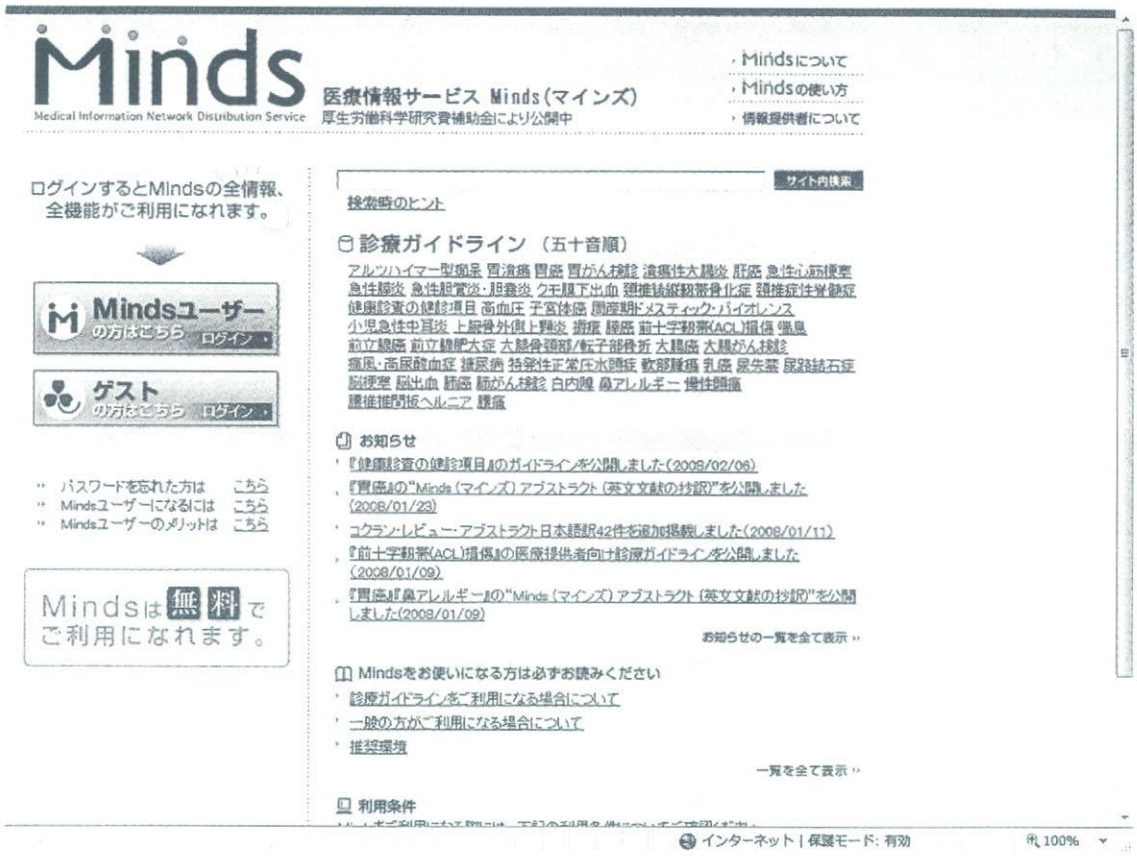

図1 医療情報サービスMindsのトップ画面

十字靱帯(ACL)損傷，喘息，前立腺癌，前立腺肥大症，大腿骨頸部/転子部骨折，大腸癌，大腸がん検診，糖尿病，特発性正常圧水頭症，軟部腫瘍，乳癌，尿失禁，尿路結石症，脳梗塞，脳出血，肺癌，肺がん検診，白内障，鼻アレルギー，慢性頭痛，腰椎椎間板ヘルニア，腰痛の43疾患(五十音順)が公開されている．また，一般向けガイドラインとしては，胃潰瘍，胃癌，急性心筋梗塞，クモ膜下出血，健康診査の健診項目，喘息，前立腺肥大症，大腸癌，尿失禁，脳梗塞，白内障，鼻アレルギーの12疾患の診療ガイドラインと関連情報がインターネット上で公開されている(http://minds.jcqhc.or.jp/)．

そのトップ画面を**図1**に示す．Mindsは通常のホームページスタイルで情報を閲覧できる'静的ページ'と，データベース構造を重視して情報間の関係を詳細に吟味できる'動的ページ'の2つの構造を有しているが，トップページから'胃癌'をクリックすると，静的ページを直ぐに閲覧できる(**図2**)．動的ページはログインをして利用が可能である(**図3**)．提供情報は，'胃がん治療ガイドラインの解説．胃がんの治療を理解しようとするすべての方のために．一般用2004年12月改訂'，'胃癌治療ガイドライン(医師用)2004年4月改訂[第2版]を同学会のご厚意により転載'というガイドラインのほかに，'MindsPLUS/医療提供者向け'としてMindsが独自に作成した情報の提供を行っている．最新の医学論文を構造化抄録形式で提供する'Mindsアブストラクト'には無作為比較臨床試験(RCT)を中心に15論文が掲載されている．また，後述するように久保田哲朗慶大教授によるCPGレビューが掲載されている．

ユーザ登録を行った利用者は平成20年1月末時点で約3万人であり，その20％は医療者でない一般の利用者である．本サイトを通じて，我が国における診療ガイドラインの普及が進むことが期待されている．

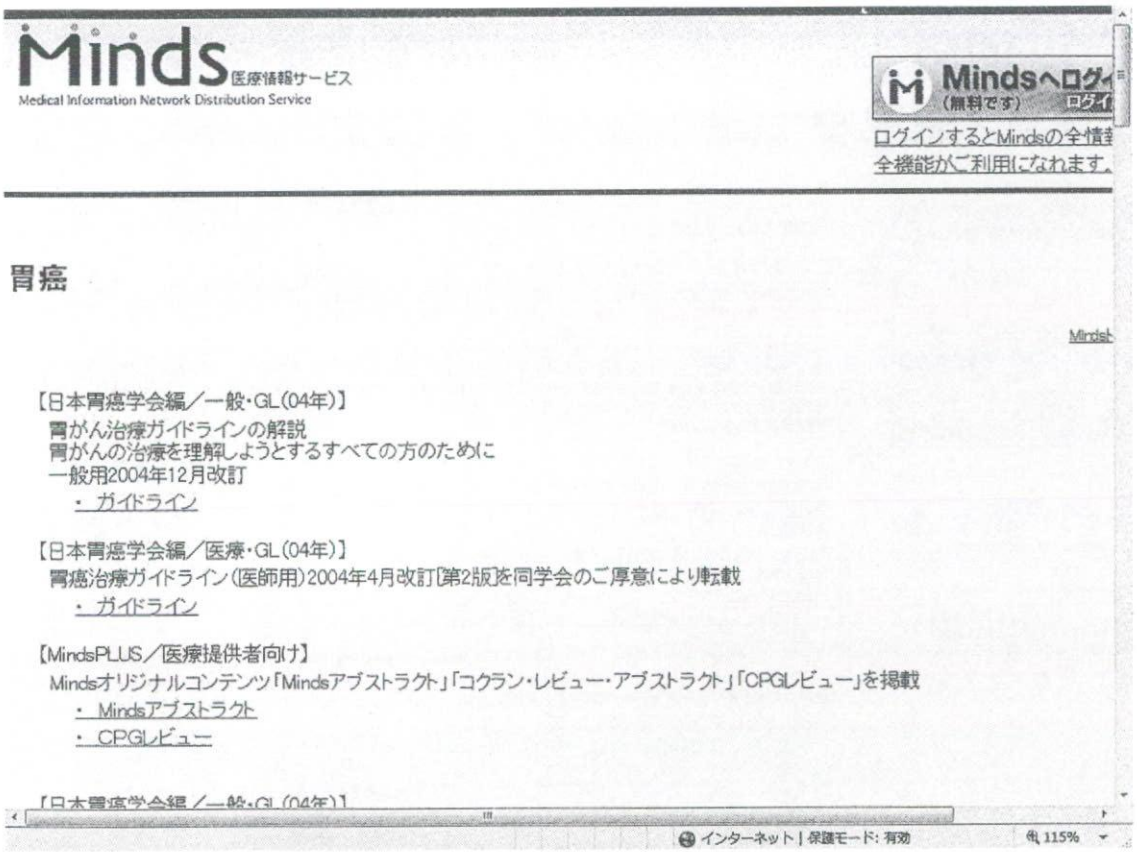

図2 胃癌に関するMindsの提供情報(静的ページ)

2. 胃癌学会'胃癌治療ガイドライン'のMindsでの情報提供

胃癌学会は平成13年に'胃癌治療ガイドライン医師用'[1]を出版した．Mindsには，'胃癌治療ガイドライン医師用，改訂第2版(2004年4月改訂)'[2]が，胃癌学会の許諾を受けて平成18年2月に公開された．更に，一般向けに作成された'胃がん治療ガイドラインの解説．胃がんの治療を理解しようとするすべての方のために'(2004年12月改訂)[3]を平成18年11月に胃癌学会の許諾を受けて掲載した．

'胃がん治療ガイドラインの解説(以下，ガイドライン解説)'の特徴をあげると，第一に，対象者を明確に胃癌と診断された患者と家族に絞っている点である．したがって，胃癌に関する一般的な知識や，予防，診断に関する説明は省略して，胃癌の治療にテーマを絞っているのが大きな特徴となっている．ガイドライン解説の'ガイドラインを作った目的'の記述では，'医師ばかりでなく患者さんやその家族の方にも読んでいただいて，胃がんという病気とその治療法についてよく理解していただき，臨床の現場での医師と患者相互の意志疎通が更に良くなることを願って，この一般用のガイドラインを作成しました'と胃癌の具体的な治療の進め方について，医師と患者の意志疎通を良くすることがあげられている．

ガイドラインの位置づけについては，'このガイドラインは胃がん治療の大まかな流れを示すもので，絶対的な治療方針を示すものではありません'とし，ガイドラインが胃癌診療や研究の進歩とともに改訂されること，個々の患者にとっての最良の治療と常に一致するとはかぎらないこと，ガイドラインの記述内容については日本胃癌学会が責任を負うが，個々に受けられる治療については，担当医師と施設の責任において実行されることが明確に記述されている．

ガイドライン解説には，'ガイドラインを理解するための基礎知識'の記述が充実している

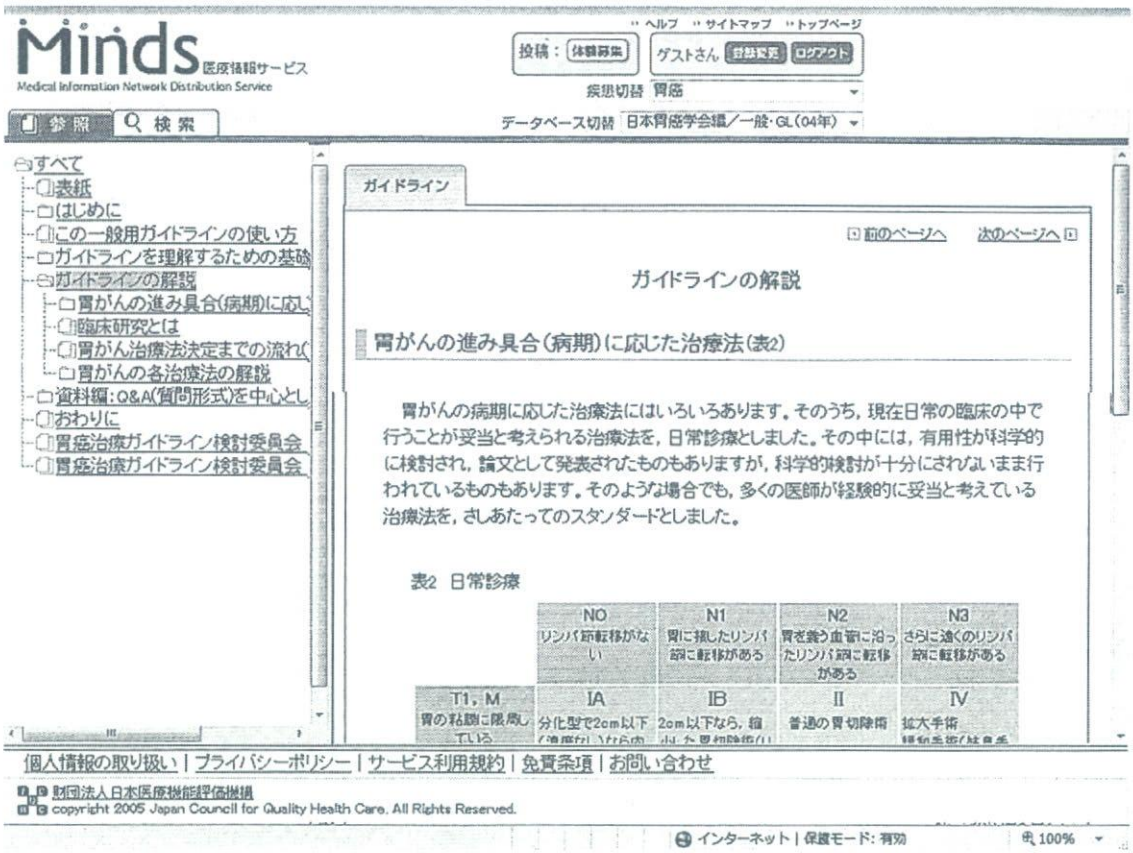

図3　Minds 動的ページに掲載された‘胃がん治療ガイドラインの解説’

のも特徴となっている．基礎知識の説明では，多くの図が使われており，解剖学の基礎知識がない患者・家族でも，胃癌の治療法の正しい理解に必要な基礎知識を効果的に学ぶことができるように配慮されている．特に胃癌の進行度と治療法の選択について，正しく理解するための配慮として血行性転移，リンパ節転移，腹膜播種に関する丁寧な説明がなされており，リンパ節郭清を含めた外科手術の選択について十分な理解が得られるように配慮されている．

更に，治療法の選択については，標準的な治療法（日常診療）と研究段階の治療法があることを解説している点も大きい．ガイドライン解説に掲載されたこの治療法の解説表は，基本形式は医師用と同一であるが，患者の理解を助けるための色使いと表現方法に工夫が施されている．臨床医から実際にこの表を用いて治療の説明を行っているとの報告も耳にする．

更に，患者・家族の理解を助けるために資料編にはQ & A（質問形式）の解説が25のテーマに関して提供されている．この中には，手術後の食事の仕方など，生活面の注意を含めて，clinical question のみでなく，patient question にも解説がなされている．

医療提供者向けの‘胃癌治療ガイドライン’との整合性が重視されている点も大きな特徴であり，2004年の医療提供者向けガイドラインの改訂に併せて一般向けのガイドライン解説も改訂されている．これに加え，難しい内容を理解しやすいようにとの配慮から‘再発とは？’，‘臨床試験の必要性’など，医師向けガイドラインには記載がないが，患者・家族にとって重要と考えられる項目について丁寧な説明もなされている．

2007年7月から12月までの6カ月間のMinds利用データを集計すると，1カ月のページビュー数は465,000ページであるが，その中で胃癌は22,000ページで約5％を占める．その3/4は一般向け情報の利用である．一般の方が胃癌の情報を求める要望が大きいことがデータとして