0.01). It is unclear whether patients with stage II or stage III disease benefit from treatment with UFT and whether treatment for 1 year is equivalent to treatment for 2 years.

In addition, Dr. Kato briefly presented data on adjuvant chemotherapy with platinum-based regimens that had been presented at ASCO 2004.

Dr. Ajani, professor of Medicine at the M.D. Anderson Cancer Center, spoke on "Current advances in the treatment of unresectable gastric and gastroesophageal adenocarcinoma." He touched first on ethnic differences in metabolism of fluorinated pyrimidines. S-1 contains ftorafur, which is converted by the cytochrome P450. CYP2A6 is responsible for the conversion from ftorafur to 5FU. It has been discovered that CYP2A6 polymorphism makes the enzyme very efficacious in Caucasians. For the same dose of S-1, accumulation of 5FU is higher in Caucasians than in Japanese, resulting in high frequency and high grade of toxicities. The recommended dose of S-1 in the Japanese population is 35–40 mg/m^2 twice daily, whereas that in Caucasians is 25 mg/m^2 if combined with cisplatin. It is quite important to determine the correct dose of S-1 for Caucasians.

Pharmacokinetic and pharmacodynamic analysis showed a clear relationship between the AUC of 5FU and grade 1 frequency of any dose-limiting toxicity. The recommended dose for Caucasians was 25 mg/m^2, twice daily, S-1 and 75 mg/m^2 cisplatin, a combination that showed a high response rate in gastrointestinal carcinoma.

Dr. Ajani presented recent results of a docetaxel-containing regimen in gastric cancer. In phase III of V325, all 463 patients have been enrolled. A planned interim analysis was carried out when 162 TTP (time-to-tumor-progression) events occurred. By this time 232 patients have been accrued. The following results of an interim analysis were presented at the proceedings of ASCLO in June 2003. All patients had advanced, untreated gastric cancer. Patients with potentially resectable primary cancer were not eligible for the study. Patients were stratified according to the level of weight loss, presence or absence of liver and peritoneal metastases, presence or absence of the primary carcinoma, and by center. Once patients signed an informed consent, they were registered and randomized to receive either DCF or CF. The doses and schedule of the DCF arm were: docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-fluorouracil 750 mg/m^2 per day as continuous infusion on days 1–5 repeated every 3 weeks. The doses and schedule for the CF arm were: cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 per day as continuous infusion on days 1–5, given every 4 weeks. Even though the two regimens had different cycles, the response assessments were synchronized. This removed the bias in TTP assessments. All responses were independently reviewed and confirmed. TTP was the primary endpoint, and overall survival (OS) of the patients was the main secondary endpoint. Currently, results on 232 patients (115/117 in DCF/CF) are available, constituting the results of a planned interim analysis. The median age was 54 years, and 98% of the patients had metastatic cancer. The median administered dose intensity calculated by dose/week basis for 5-fluorouracil and cisplatin was the same for DCF and CF. The TTP was statistically superior ($P = 0.0008$) for DCF (5.2 months compared with 3.7 months for CF). This meant that patients receiving DCF had a 70% lower chance of having cancer progression than those receiving CF. The median survival time was longer for patients receiving DCF (10.2 months) than those receiving CF (8.5 months) ($P = 0.0064$). This meant that patients receiving DCF had a 50% lower risk of death than those receiving CF during the study. This P value did not cross the preset boundary at the interim analysis, but the conditional probability of DCF having a statistically median survival time superior to CF is 99.4%. The response rate was 39% for DCF and 23% for CF. This difference is statistically superior ($P = 0.012$). DCF can result in bone marrow suppression and increased risk of infection. Thus, neutropenic fever and the neutropenic infection rate, as expected, were higher from DCF than from CF. DCF can also cause diarrhea and mucositis. Careful patient selection is highly recommended. In addition, aggressive management of the side effects of DCF is essential. DCF should now be offered to all patients with advanced gastric or gastroesophageal junction cancer who are in good general condition. Further development of this regimen is also warranted. The V325 study was sponsored by Aventis. Recent data from Roth et al. (ASCO noncolorectal GI presentation in 2004) also demonstrated that the combination of docetaxel, cisplatin, and 5-flurouracil had a higher response rate and longer time-to-progression than docetaxel plus cisplatin, or epirubicin, cisplatin, and 5-flurouracil. The SAKK group has now decided to compare docetaxel, cisplatin, and 5-fluorouracil (as the experimental arm) with epirubicin, cisplatin, and 5-fluorouracil ("ECF" as a reference regimen). Thus two separate studies seem to establish the value of docetaxel in patients with advanced gastric or gastroesophageal adenocarcinoma.

Dr. Sasako, chief of surgery, National Cancer Center Hospital, presented results of surgical procedures in operable stomach cancer. In many solid tumors, surgery remains the major part of the treatment with curative intent. To establish a better standard treatment, many clinical trials have been carried out on multidisciplinary treatments, including surgery, and some on purely surgical procedures. Unlike drug treatment, the results of surgery are often hampered by the heterogeneity in the quality of treatment. The results of surgery are affected by the surgeons' skill, experience (learning curve), and personal preference. Experience includes not only the quality of surgery but also that of postoperative care. A Dutch trial on D2 dissection for gastric cancer provided a good example by showing the difficulty and importance of quality control of surgery and postoperative care. In this trial, more than 28% of patients who developed major complications died, whereas death occurred in only 9% of such patients in a Japanese specialist center, most likely due to lack of knowledge and experience of managing complications in participating hospitals. It seems that the hospital volume per year, while it was as small as 1.0 on average, was insufficient for carrying out D2 dissection safely. The impact of a significantly larger proportion of treatment-related deaths after D2 dissection was

too large to be redeemed by the treatment effect in the long term. This was also the case in two clinical trials on esophageal cancer in France and Germany reported in the 2003 ASCO meeting.

In the IT-0116 trial on adjuvant treatment of gastric cancer, adjuvant chemoradiotherapy (CRT) after curative surgery was shown to improve the survival of patients with gastric cancer. In this trial, 50% of patients underwent D0 dissection, 40% had D1, and only 10% had D2, in spite of the description of the protocol. Therefore, the results of this trial suggest that adjuvant CRT is effective for those who underwent limited surgery and for whom limited surgery is not a sufficient treatment for curable gastric cancer. From the large database of lymph node metastasis in Japanese patients, limited surgery theoretically often leaves metastatic nodes unresected, thus leading to recurrence. An in-depth analysis of this trial showed that surgical under treatment was an independent prognostic factor. This trial clearly showed that the effects of adjuvant treatment can differ depending on the type of surgery. To evaluate the efficacy of adjuvant treatment, the type of surgery should be defined in the protocol, and strict quality control of surgery is mandatory. Through the experience of planning and carrying out clinical trials on surgical treatment of malignant diseases inside and outside of Japan, the key issues in surgical trials on cancer treatment were discussed.

Dr. Blumgart, professor of surgery, Cornell University Medical College, spoke on "Surgical advances in hepatobiliary cancer." He focused his talk on hepatic resection. Hepatectomy has a long history, starting with a record of 1801 liver resections. Compared with results in the early twentieth century, blood loss has significantly decreased to about 500ml, segmental resections have been developed, and the transfusion rate and operating time were down at the beginning of the twenty-first century. Even if the tumor is large and hepatocellular cancer invades a major vessel, the 5-year survival rate was 37% in 412 patients treated from 1991 to 1998 at Memorial Sloan-Kettering Cancer Center (MSKCC). Tumor size is closely related to patient prognosis.

Dr. Blumgart mentioned the indications for liver transplantation after partial hepatectomy. The objective was to determine the survival and recurrence pattern of the partial hepatectomy for patients with hepatocellular carcinoma (HCC) who have been selected for transplantation. In MSKCC, among 611 cases, 180 were resectable but only 36 (20%) met the Milan Criteria. The operative mortality of these 36 patients receiving partial hepatectomy with transplantation was 2.8%. In 20 recurrent cases, the 5-year survival rate was 57%, and for 14 no-recurrence patients, it was 93%. From these results, partial hepatectomy for patients otherwise eligible for transplant can be performed with reasonable morbidity and mortality.

Hepatic resection for metastatic colorectal cancer was not justified in the early 1950s because metastases are nearly always multiple. Although there is no randomized controlled trial to solve the problem of this issue, retrospective analysis demonstrates that resected cases showed a high survival rate compared with nonresected cases (38% vs 0%). At MSKCC, 1001 resections were conducted for metastatic hepatic carcinomas, and the number of 5-year survivors reached 136. Perioperative mortality was 2.8%, the 5-year survival rate 39%, and the 10-year survival rate 23%. Five clinical risk factors were identified by multivariate analysis: (1) node positive primary, (2) disease-free interval less than 12 months, (3) more than one tumor, (4) tumor size more than 5cm, and (5) CEA greater than 200ng/ml. These factors are important for patient selection and stratification in clinical trials.

Although the majority of the symposium topics concentrated on surgery, including lung cancer, gastrointestinal cancers, and hepatobiliary cancer, the peak number of attendees was less than 200; by the end of symposium it was less than 50. ASCO and JSCO were disappointed again with their joint scientific symposium. In the JSMO meeting it is possible for us to attract audiences of 700–1000. In 2005, JSCO will organize a symposium on the topic of "The Role of Board-Certified Medical Oncologists."

Surgically Curable Peripheral Lung Carcinoma*

Correlation of Thin-Section CT Findings With Histologic Prognostic Factors and Survival

Kunihiko Shimizu, MD; Kouzou Yamada, MD; Haruhiro Saito, MD; Kazumasa Noda, MD; Haruhiko Nakayama, MD; Youichi Kameda, MD; and Koichiro Nakata, MD

Study objectives: **To define characteristics of surgically curable, early cancers of the lung, we retrospectively studied relationships between thin-section CT (TS-CT) scans, pathologic features, and outcome data in 287 patients with resected small-diameter (< 20 mm) peripheral lung carcinoma. Cases included 260 adenocarcinomas, 16 squamous cell carcinomas, 6 small cell carcinomas, 3 large cell carcinomas, and 2 others.**

Measurements and results: **All tumors were classified by tumor shadow disappearance rate (TDR) on TS-CT as having either an "air-containing" or "solid-density" pattern. Adenocarcinomas are typically classified into these patterns. Air-containing patterns (n = 136) showed 1% pleural involvement and 2% vascular invasion, with no lymphatic permeation by pathology. Solid-density patterns (n = 124) showed 34% pleural involvement, 42% vascular invasion, and 29% lymphatic permeation. No cases of relapse or death were observed in cases with the air-containing pattern, in contrast to the high relapse and death rate in solid-density cases ($p < 0.0001$). All non-adenocarcinoma cases (n = 25) had a solid-density pattern, with 4% pleural involvement, 52% vascular invasion, and 44% lymphatic permeation. The overall 5-year survival rate for non-adenocarcinoma was 60%, similar to that for solid-density adenocarcinoma.**

Conclusions: **When peripheral lung cancers < 20 mm in diameter show air-containing patterns on TS-CT images, surgical outcomes may be favorable with curable disease.**

(CHEST 2005; 127:871–878)

Key words: adenocarcinoma; air-containing pattern; early peripheral lung cancers; histopathologic classification; prognosis; solid-density pattern; thin-section CT

Abbreviations: BAC = bronchioloalveolar carcinoma; CR = chest radiography; GGO = ground-glass opacity; HU = Hounsfield unit; kVp = kilovolt peak; mDmax = maximum dimension of tumor using mediastinal window level setting; mDperp = largest dimension of the perpendicular axis on mediastinal window level setting; MWLS = mediastinal window level setting; pDmax = maximum dimension of tumor using pulmonary window level setting; pDperp = largest dimension of the perpendicular axis using pulmonary window level setting; PWLS = pulmonary window level setting; TDR = tumor shadow disappearance rate; TS-CT = thin-section CT

Recently, the number of patients with small peripheral lung cancers detected by CT scanning has been increasing.[1–3] In these reports, most cases have been adenocarcinoma and, more rarely, non-adenocarcinoma. Early detection of lung cancer, which can be achieved through recent advances in CT scan technology, may improve the survival rate of patients with this disease. However, the prognosis of resected lung cancer remains poor, and < 80% of stage I patients are cured by surgical resection alone.[4] Because regional lymph node involvement is found in approximately 20% of primary lung adeno-

*From the Division of Respiratory Medicine (Drs. Shimizu and Nakata), Department of Internal Medicine, Toho University School of Medicine, Tokyo; and Departments of Thoracic Oncology (Drs. Yamada, Saito, and Noda), Thoracic Surgery (Dr. Nakayama), and Pathology (Dr. Kameda), Kanagawa Cancer Center, Yokohama, Japan.

This work was supported in part by Grant for Scientific Research Expenses for Health Labour and Welfare Programs and the Foundation for the Promotion of Cancer Research, and by Second-Term Comprehensive 10-year Strategy for Cancer Control.

Manuscript received December 8, 2003; revision accepted September 29, 2004.

Correspondence to: Kunihiko Shimizu, MD, Toho University School of Medicine, Department of Internal Medicine, Division of Respiratory Medicine, Omorinishi 6–11–1, Otaku, Tokyo, Japan; e-mail: kshimizu@med.toho-u.ac.jp

carcinomas of ≤ 2.0 cm in size, major lung resection and locoregional lymph node resection or sampling have been recommended even for small tumors.[5] Yet, tumor size is not a reliable prognostic indicator for small peripheral lung adenocarcinomas.

Histologically and biologically, adenocarcinoma of the lung constitutes a heterogeneous group of tumors; it is difficult to predict the prognosis of surgically treated patients with this disease. Recently, the size of central collapse/fibrosis[6] and the percentage of the bronchioloalveolar carcinoma (BAC) component have been proposed as prognostic indicators for small lung adenocarcinomas.[7] Although many reports on the radiologic-pathologic correlations of small lung adenocarcinoma have been published, there is little clinical information on prognostic factors during the pretreatment state. Furthermore, in cases of non-adenocarcinoma, there are no comparable definitions for early cancers. Thus, the concept of peripherally located, surgically curable, "early lung cancer" remains controversial. This study retrospectively analyzed findings obtained by thin-section CT (TS-CT) and correlated them with histologic features and outcome in patients with small-size lung cancers.

Materials and Methods

We retrospectively reviewed the records and CT images of 287 patients with peripheral lung cancers < 20 mm in diameter between 1992 and 2002. The majority of patients were found by screening for lung cancer. Those found by chance during follow-up of other diseases were the second most common. The patients who visited our hospital with complaints suggestive of lung cancer ranked third. Informed consent was obtained from each patient before operation. Chest CT images were obtained by an X-Vigor/Real CT scanner (Toshiba Medical Systems; Tokyo, Japan). Conventional CT images were obtained serially from the thoracic inlet to the lung bases at 120 kilovolt peak (kVp) and 200 mA, with 10-mm section thickness, 10-mm section spacing, 512 × 512 pixel resolution, and 1-s scanning time. High-resolution images targeted to the tumor were obtained serially at 120 kVp and 200 mA, with 2-mm section thickness, pitch 1, 1- to 2-mm section spacing, 512 × 512 pixel resolution, and 1-s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. These images were printed as photographs on each sheet of film using a mediastinal window level setting (MWLS; level, 40 Hounsfield units [HU]; width, 400 HU) and a pulmonary window level setting (PWLS; level, − 600 HU; width, 1,600 HU).

While contrast medium (60 mL) was infused IV during imaging, lesion sites were translocated in a helical scan mode with a CT table speed of 2 mm/s; TS-CT images were obtained at 1 breath-holding (120 kVp, 200 mA). The time interval between CT examination and subsequent surgery was < 2 weeks in all patients. All CT images were reviewed by four thoracic oncologists who were not informed of the pathologic findings. They obtained the following information from the TS-CT images: the maximum dimension of tumor using PWLS (pDmax), the largest dimension of the perpendicular axis using PWLS (pDperp), the maximum dimension of tumor using MWLS (mDmax), and the largest dimension of the perpendicular axis on MWLS (mDperp).

We defined the tumor shadow disappearance rate (TDR) using the following formula (Fig 1): TDR = 1 − (mDmax × mDperp/pDmax × pDperp).[8] TDRs of ≥ 50% vs < 50% were considered to represent air-containing and solid-density patterns, respectively.[9] Ground glass opacity (GGO) was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures.[10] Examples of CT images of the two groups are shown in Figures 2–4.

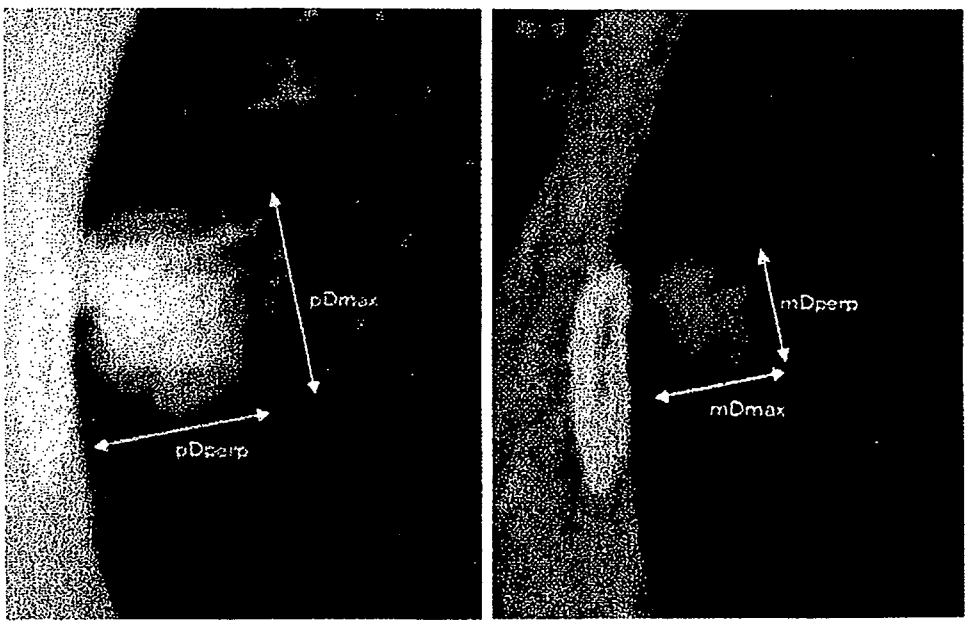


FIGURE 1. Air-containing type of adenocarcinoma (18 × 18 mm) in the right upper lobe. We measured pDmax and pDperp on PWLS images (*left*) and mDmax and mDperp on MWLS images (*right*).

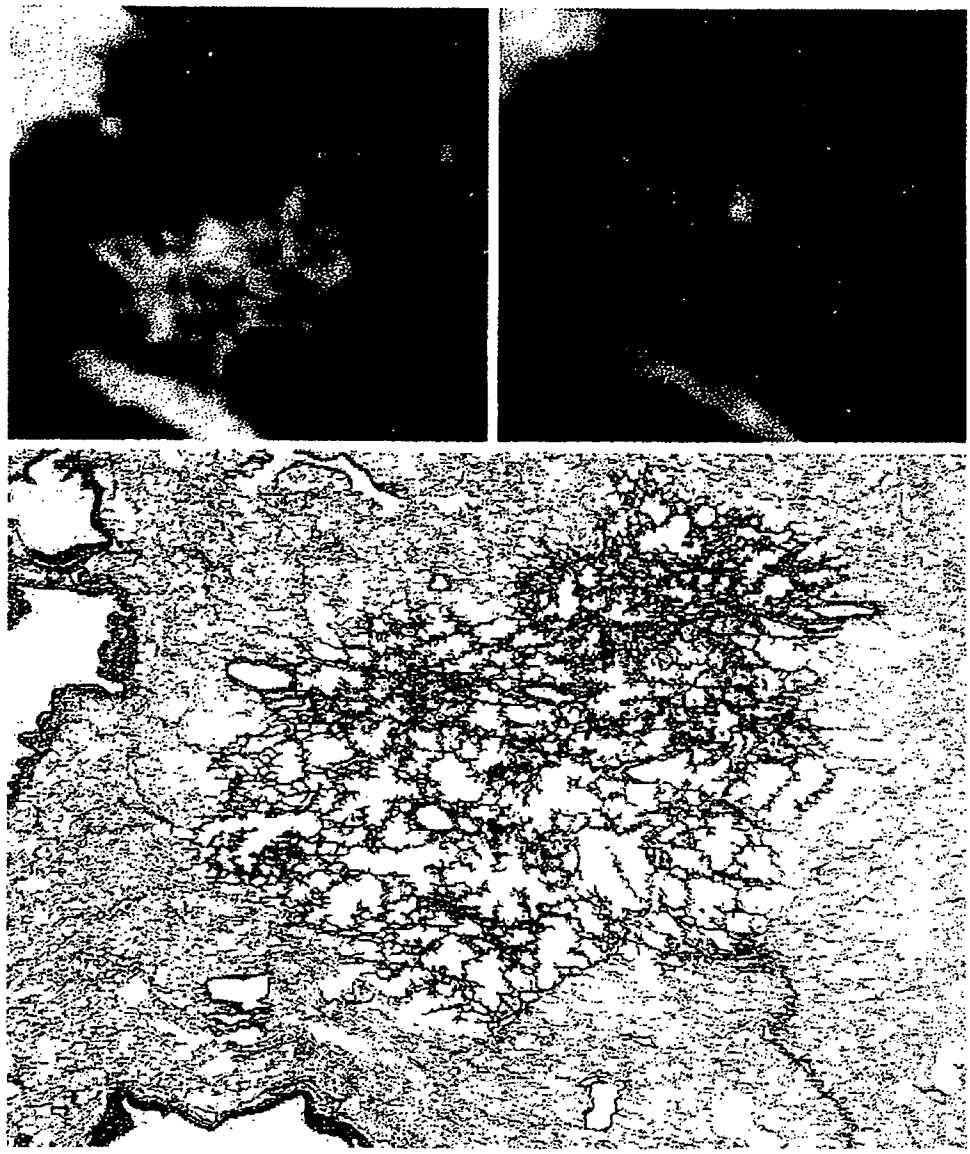


FIGURE 2. Air-containing type of adenocarcinoma (20 × 19 mm) in the left lower lobe. *Top left* and *top right*: The value of TDR in this adenocarcinoma was 10%. *Bottom*: Histologic section shows localized bronchioloalveolar carcinoma without alveolar collapse (hematoxylin = eosin, original × 6).

Each pattern based on TS-CT images was evaluated in terms of pathologic findings and survival outcome. We evaluated pathologic TNM (patholic stage), pleural involvement, vascular invasion, and lymphatic permeation. In addition, the pathologic subtypes according to the classification of Noguchi et al[11] of small adenocarcinoma of the lung were evaluated. The length of survival was defined as the interval in months between the date of surgical resection and the date of last follow-up or death due to any cause.

Statistical analyses were carried out using the generalized Wilcoxon test and log-rank test. Statistical significance was accepted at a $p < 0.05$. Relapse-free and overall survival rates were estimated by the Kaplan-Meier method.[12]

RESULTS

Patient characteristics are summarized in Table 1. A total of 287 patients (128 men and 159 women; age range, 26 to 86 years; mean age, 65 years) were included in the study, and consisted of 260 cases of adenocarcinoma and 27 cases of non-adenocarcinoma (16 squamous cell, 6 small cell, 3 large cell, and 2 of other histology). Among the adenocarcinoma cases, there were 62 cases with the largest diameter of the lesion < 10 mm, 88 cases were 10 to 15 mm, and 110 cases were 16 to 20 mm.

Chest radiography (CR) and CT detected 155 cases and 132 cases, respectively, of chest lesions < 20 mm in diameter. With respect to the chance of detection and initial size, 11 cases and 51 cases of lesions < 10 mm in diameter were detected by CR and CT, respectively. Correspondingly, 42 cases and 46 cases of lesions 10 to 15 mm in diameter and 82 cases and 28 cases of lesions 16 to 20 mm in diameter

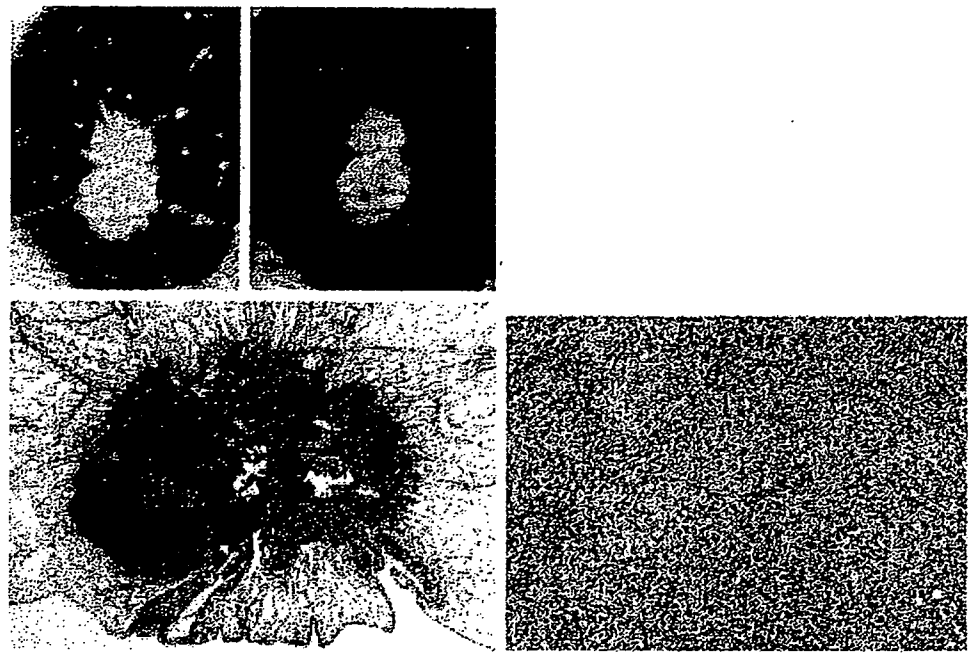


FIGURE 3. Solid-density type of adenocarcinoma (19 × 8 mm) in the right upper lobe. *Top left* and *top right*: The value of TDR in this adenocarcinoma was 90%. *Bottom left*: Histologic section shows a poorly differentiated adenocarcinoma (hematoxylin = eosin, original × 6). *Bottom right*: Same as previous image (*bottom left*) but with higher magnification (hematoxylin = eosin, original × 200).

were detected, respectively. Among non-adenocarcinoma cases, seven were initially detected by CT; however, these tumors were also detected by CR.

Table 2 shows the relationship between classification according to TS-CT images and pathologic findings of the adenocarcinoma cases. The number of cases with an air-containing pattern was 136, and the number of cases with a solid-density pattern was

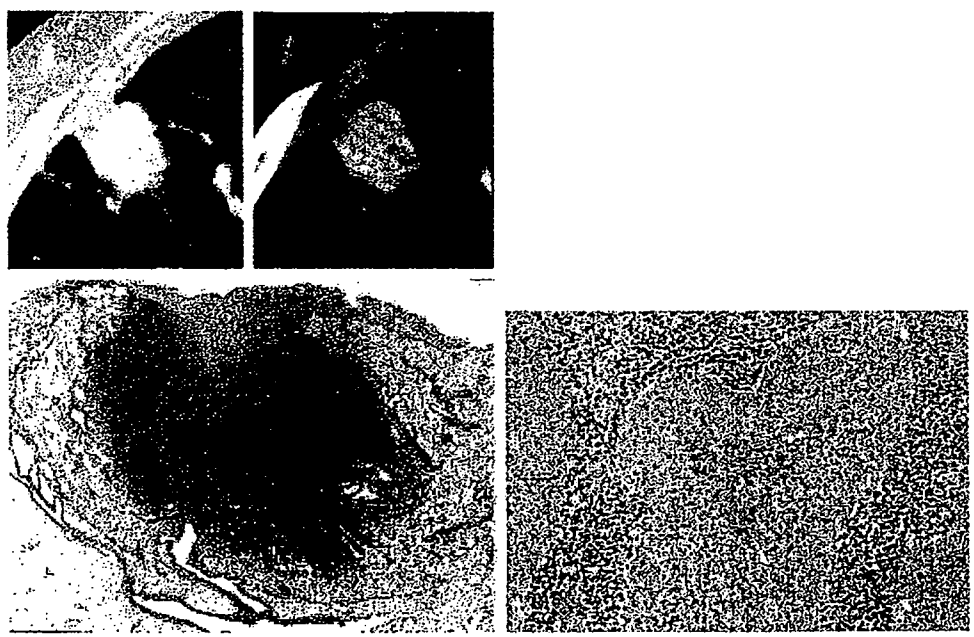


FIGURE 4. Solid-density squamous cell carcinoma (18 × 16 mm) in the right upper lobe. *Top left* and *top right*: The value of TDR in this carcinoma was 95%. *Bottom left*: Histologic section reveals moderately differentiated squamous carcinoma (hematoxylin = eosin, original × 6). *Bottom right*: Same as previous image (*bottom left*) but with higher magnification (hematoxylin = eosin, original × 200).

Table 1—*Characteristics of 287 Patients With Small Peripheral Carcinomas of the Lung*

Characteristics	All	Adenocarcinoma*	Non-Adenocarcinoma†
Male/female gender, No.	128/159	105/155	23/4
Age range, yr (median)	26–86 (65)	26–86 (65)	49–80 (67)
Initial detection			
CR/CT	155/132	135/125 11/51 (< 10 mm) 42/46 (10–15 mm) 82/28 (> 16 mm)	20/7
Tumor diameter range (median), mm	3–20 (15.9)	3–20 (15)	7–20 (16.8)

*Noguchi classification: type A (n = 37), type B (n = 55), type C (n = 129), type D (n = 22), type E (n = 2), and type F (n = 15).[11]
†Histology: squamous cell carcinoma (n = 16), small cell (n = 6), large cell carcinoma (n = 3), other (n = 2).

124. Among air-containing cases, 1% had pleural invasion, 2% had vascular invasion, and 0% had lymphatic permeation. Among solid-density cases, 42 cases (34%) had pleural involvement, 53 cases (42%) had vascular invasion, and 36 cases (29%) had lymphatic permeation. All cases with an air-containing pattern were pathologic stage IA, in contrast to only 71% of cases with a solid-density pattern.

Table 3 shows the relationship between TS-CT classification and the Noguchi pathologic classification.[11] In the air-containing pattern, almost all of types A and B, and 40% of type C cases were included, and no cases of type D and E and F were included. In contrast, all of types D and E and F and 60% of type C were included in the solid-density pattern. Two cases of type A were also included in this pattern, and these proved to be mucocellular adenocarcinomas, which explains their high density on TS-CT images. Of the 260 adenocarcinoma patients, 169 underwent lobectomy and 2 underwent pneumonectomy, while 89 patients underwent segmental and wedge resections combined with systematic hilar and mediastinal node dissection. In the 89 patients who did not have complete resection, 60 showed air-containing patterns and 29 were solid-density patterns. The 60 patients with an air-containing pattern had intentional limited resection because of their small size, while the 29 patients with a solid-density underwent compromised limited resection because of age or pulmonary hypofunction.

Table 2—*TS-CT Findings, Pathologic Involvement, and Stage in 287 Peripheral Adenocarcinomas**

	TS-CT Findings		
	Adenocarcinoma		Non-adenocarcinoma
Pathologic Findings	Air	Solid	Solid
Pleural involvement			
Absent/present	135 (99)/ 1 (1)	82 (66)/ 42 (34)	26 (96)/ 1 (4)
Vascular invasion			
Absent/present	133 (98)/ 3 (2)	71 (58)/ 53 (42)	12 (44)/ 15 (56)
Lymphatic permeation			
Absent/present	136 (100)/ 0 (0)	88 (71)/ 36 (29)	14 (52)/ 13 (48)
Pathologic stage			
IA/≥ IB	136 (100)/ 0 (0)	89 (71) /35 (29)	22 (81)/ 5 (19)

*Data are presented as No. (%).

Table 3—*TS-CT Findings, by TDR Type, of 260 Small-Sized Peripheral Adenocarcinomas Correlated With Pathologic Classification**

	TS-CT Findings	
Noguchi Type	Air (n = 136)	Solid (n = 124)
A	35 (26)	2
B	46 (34)	9
C	55 (40)	74 (60)
D	0	22 (18)
E	0	2
F	0	15 (12)

*Classification of Noguchi et al.[11] Data are presented as No. (%) or No.

The overall and relapse-free survival of patients with adenocarcinoma from the time of surgery are shown in Figures 5 and 6, respectively. The air-containing pattern had a 100% 5-year survival rate, and relapse-free survival was significantly better than that of solid-density cases ($p < 00001$, generalized Wilcoxon test and log-rank test). There were no

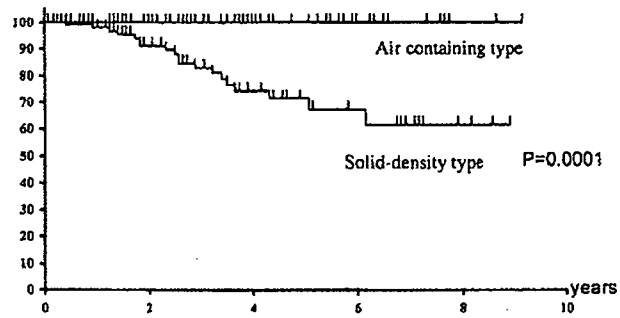


FIGURE 5. Overall survival curves of patients with small adenocarcinomas. No deaths were observed in patients with air-containing tumors; survival in the solid-density type declined progressively. The 5-year survival rate of patients with solid-density type was 60%.

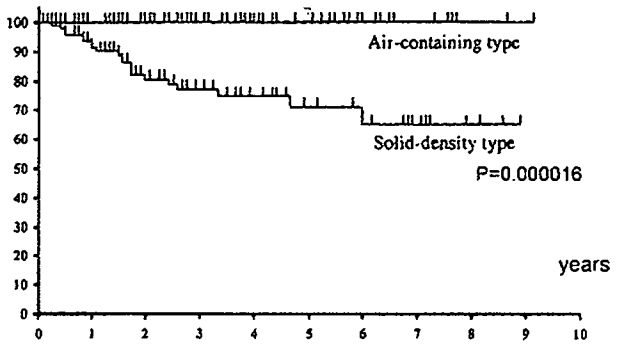


FIGURE 6. Relapse-free survival curve shows a significant difference between the two groups described in Figure 6.

recurrences in patients with air-containing lesions. Intentional limited resection is therefore considered to be adequate for type A and B lesions, which were air containing and consisted mainly of GGO.

For non-adenocarcinomas, pathologic findings included 4% pleural involvement, 56% vascular invasion, and 48% lymphatic permeation, with 81% of patients in pathologic stage IA (Table 2). The 5-year survival rate for patients with non-adenocarcinoma was 60% (Fig 7).

DISCUSSION

Tumor size in lung adenocarcinoma cancer is not as good a prognostic factor as it is for squamous cell carcinoma, we often encounter small lung adenocarcinomas that have mediastinal lymph node involvement or even distant metastasis. Peripheral lung adenocarcinomas smaller than 3 cm frequently recur, resulting in cancer deaths (5-year disease-free survival for T1N0 disease of approximately 70%).[4] It is important to established reliable prognostic factors for small peripheral lung adenocarcinoma. Consequently, qualitative analysis of tumors is required to establish prognostic criteria in addition to size.

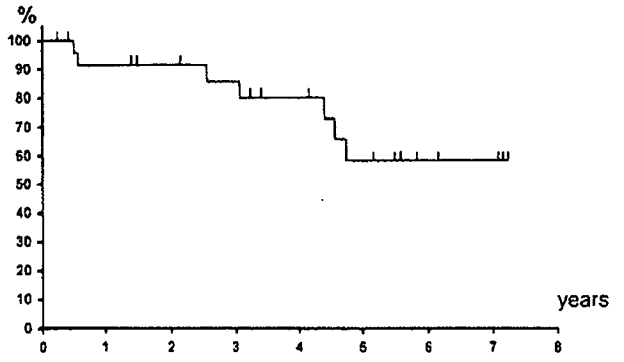


FIGURE 7. Overall survival curve of all patients with small non-adenocarcinomas. The 5-year survival rate for patients with non-adenocarcinoma was 60%.

In 1995, Noguchi et al[11] proposed a histologic classification of small lung adenocarcinomas based on the presence or absence of a bronchioloalveolar carcinoma (BAC) component. Tumors with a BAC component were further subclassified into three groups: type A, BAC without collapse or fibrosis; type B, BAC with foci of collapse; and type C, BAC with foci of active fibroblastic proliferation. Invasive carcinomas without a BAC component were subdivided into types D to F. In their report, patients with type A or type B have shown no lymph node spread and have excellent outcomes (100% 5-year survival). Therefore, prompt detection, diagnosis, and treatment of type A or type B are thought to greatly improve outcome.

However, these criteria were based on postoperative pathologic findings after resection; therefore, these cannot have an impact on the choice of treatment. Because noninvasiveness can be identified only by postoperative microscopic study, type A or type B must be selected by preoperative TS-CT images. We have analyzed TS-CT images of lung adenocarcinoma using TDR. We found most of types A and B and 40% of type C have the air-containing pattern, whereas all of types D, E, and F and 60% of type C are included in the solid-density pattern. The air-containing pattern has a 100% 5-year survival rate, and relapse-free survival was significantly better than that of solid-density cases.

As for the air-containing pattern, type A and B lesions have shown mostly GGO in TS-CT images and have lacked solid components. Pathologic analyses have revealed a replacing growth pattern of tumor cells along the alveolar septa, with a subsequent BAC pattern. Kuriyama et al[13] quantitatively evaluated the extent of GGO in pulmonary adenocarcinoma with types A, B, and C and found that it was significantly greater in types A and B than in type C adenocarcinoma. However, it has been difficult to distinguish types A and B from type C using TS-CT images, specially since the presence of fibroblastic proliferation was the only differentiating factor. Although the Noguchi classification defines a surgically curable subset of peripheral lung adenocarcinomas (types A and B), the criteria for active fibroblasts remains undefined.[14] In addition, type C tumors account for the majority of small lung adenocarcinomas, suggesting that these tumors may represent a heterogeneous group with a spectrum ranging from minimally invasive to overtly invasive cancer.[15]

If patients who have favorable prognoses are chosen from the whole population of those with type C cancers and selectively treated, the overall prog-

nosis of patients with small pulmonary adenocarcinoma would improve. Suzuki et al[6] and Higashiyama et al[16] found a subgroup of type C cancers associated with a good prognosis. In our study, we found that type C cases present with both air-containing and solid-density patterns. It was conceived that the BAC component in the peripheral region was predominant in type C cancers with an air-containing pattern, whereas fibrotic scar in the central region was predominant in those classified as solid density. We might have isolated those cases with a good prognosis by classifying type C lesions according to the air-containing pattern; however; we would then have been unable to distinguish types A, B, and C according to pathologic type.

Types D, E, and F have images that characteristically show a sharp margin and lobular structures without GGO components on TS-CT images. These findings are consistent with the solid-density pattern. The values of TDR in types D, E, and F were 0%, which reflects that the images consisted only of solid components. The relationship between the CT image pattern of lung cancer and pathologic stage revealed that all air-containing cases belonged to stage IA, while > 20% of solid-density cases belonged to stage IB or a more advanced stage.

Ichinose et al[17] examined surgically treated cases of non-small cell lung cancer with diameters < 10 mm and reported that even patients with pathologic stage IA have high rates of lymphatic invasion. However, we found that adenocarcinoma cases with an air-containing pattern have no lymphatic permeation, and pleura or vascular invasion occurred in as few as 1 to 2% of patients. However, 20 to 30% of adenocarcinoma cases with solid-density patterns show pleural involvement, lymphatic permeation, or vascular invasion. We conclude that patients with adenocarcinoma with a solid-density pattern have an unfavorable prognosis for postoperative survival; their 5-year survival rate is 60% compared with 100% of cases with an air-containing pattern.

Among patients with stage IA adenocarcinoma, 136 cases exhibited an air-containing pattern and 89 were solid density. All of 136 patients with IA air-containing lesions survived, and recurrence was not found any of them. In contrast, cancer recurred in 14 of 89 patients with IA solid-density lesions, and 10 of the 14 patients died. Patients with IA solid-density lesions therefore should benefit from adjuvant therapy.

Among patients with non-adenocarcinoma, no cases with air-containing patterns were shown on TS-CT imaging (Fig 4). Patients with non-adenocarcinoma have various types of histology and are too few in number to accurately evaluate their prognosis. The non-adenocarcinoma cases had low rates of pleural involvement, but high rates of vascular invasion, and lymphatic permeation. Survival curves of patients with non-adenocarcinoma resemble those of patients with adenocarcinoma of a solid-density pattern. We could not identify any subset of patients with non-adenocarcinoma who showed favorable outcomes using TS-CT images.

According to recent reports of serial changes in the appearance of BAC on CT, localized GGO can change into mixed areas of GGO and solid components, and solid components can increase over time.[18,19] We suspect that adenocarcinoma with a larger GGO area is at an early and curable stage; TS-CT findings may predict this outcome.

Conclusion

Air-containing adenocarcinoma patterns may correspond to an early stage of disease when they occur in the periphery of the lung and are < 20 mm in diameter.

References

1 Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996; 201:798–802

2 Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998; 351:1242–1245

3 Henschke CI, McCauley DI, Yankelevits DF, et al. Early lung cancer action project: overall design and findings from baseline screening. Lancet 1999; 354:99–105

4 Thomas PA, Piantadosi S. Postoperative T1N0 non-small cell lung cancer: squamous versus non-squamous recurrences. J Thorac Cardiovasc Surg 1987; 94:349–354

5 Asamura H, Nakayama H, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell-lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996; 111:1125–1134

6 Suzuki K, Yokose T, Yoshida J, et al. Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 2000; 69:893–897

7 Yokose T, Suzuki K, Nagai K, et al. Favorable and unfavorable morphological prognosis factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. Lung Cancer 2000; 29:179–188

8 Takamochi K, Nagai K, Yoshida J, et al. N0 status in pulmonary adenocarcinoma is predictable by combining serum carcinoembryonic antigen level and computed tomographic findings. J Thorac Cardiovasc Surg 2001; 122:325–330

9 Kondo T, Yamada K, Noda K, et al. Radiologic-prognostic correlation in patients with small pulmonary adenocarcinomas. Lung Cancer 2001; 36:49–57

10 Austin JHM, Muller NL, Friedman PJ, et al. Glossary of terms for CT of the lung: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 1996; 200:327–331

11 Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocar-

cinoma of the lung: histologic characteristics and prognosis. Cancer 1995; 75:2844–2852
12 Kaplan EK, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958; 53:457–481
13 Kuriyama K, Seto M, Kasugai T. Ground-glass opacity on thin-section CT: value in differentiating subtype of adenocarcinoma of the lung. AJR Am J Roentgenol 1999; 173:465–469
14 Maeshima A, Niki T, Maeshima A, et al. Modified scar grade: an indicator in small peripheral lung adenocarcinoma of the lung. Cancer 2002; 95:2546–2554
15 Terasaki H, Niki T, Matsuno Y, et al. Lung adenocarcinoma with mixed bronchioloalveolar and invasive components: clinicopathological features, subclassification by extent of invasive foci, and immunohistochemical characterization. Am J Surg Pathol 2003; 27:937–951
16 Higashiyama M, Kodama K, Yokouchi H, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. Ann Thorac Surg 1999; 68:2069–2073
17 Ichinose Y, Yano T, Yokoyama H, et al. The correlation between tumor size and lymphatic vessel invasion in resected peripheral stage 1 non-small cell lung cancer. J Thorac Cardiovasc Surg 1994; 108:684–686
18 Jang HJ, Lee KS, Kwon OJ, et al. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. Radiology 1996; 199:485–488
19 Aoki T, Tomoda Y, Watanabe H, et al. Peripheral lung adenocarcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001; 804:803–809

Cancer Chemother Pharmacol (2005) 56 (Suppl 1): s90–s93
DOI 10.1007/s00280-005-0104-6

Kazuto Nishio · Tokuzo Arao · Tatsu Shimoyama · Yasuhiro Fujiwara · Tomohide Tamura · Nagahiro Saijo

Translational studies for target-based drugs

Published online: 5 November 2005

Abstract The biological background for the clinical and prognostic heterogeneity among tumors within the same histological subgroup is due to individual variations in the biology of tumors. The number of investigations looking at the application of novel technologies within the setting of clinical trials is increasing. The most promising way to improve cancer treatment is to build clinical research strategies on intricate biological evidence. New genomic technologies have been developed over recent years. These techniques are able to analyze thousands of genes and their expression profiles simultaneously. The purpose of this approach is to discover new cancer biomarkers, to improve diagnosis, predict clinical outcomes of disease and response to treatment, and to select new targets for novel agents with innovative mechanisms of action. Gene expression profiles are also used to assist in selecting biomarkers of pharmacodynamic effects of drugs in the clinical setting. Biomarker monitoring in surrogate tissues may allow researchers to assess "proof of principle" of new treatments. Clinical studies of biomarkers monitoring toxicity profiles have also been done. Such pharmacodynamic markers usually respond to treatment earlier than clinical response, and as such may be useful predictors of efficacy. Epidermal growth factor receptor (EGFR) mutation in lung cancer tissues is a strong predictive biomarker for EGFR-targeted protein tyrosine kinase inhibitors. Monitoring of EGFR mutation has been broadly performed in retrospective and prospective clinical studies. However, global standardization for the assay system is essential for such molecular correlative studies. A more sensitive assay for EGFR mutation is now under evaluation for small biopsy samples. Microdissection for tumor samples is also useful for the sensitive detection of EGFR mutation. Novel approaches for the detection of EGFR mutation in other clinical samples such as cytology, pleural effusion and circulating tumor cells are ongoing.

Keywords Biomarker · Proof of principle · Pharmacodynamic marker · EGFR mutation

This work was presented at the 20th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Concepts of Treatment Strategies for Hormone-Related Cancer", 11–12 March 2005, Nagoya, Japan.

K. Nishio (✉) · T. Arao · T. Shimoyama
Shien Lab, National Cancer Center Hospital,
Tsukiji 5–1–1, Chuo-ku, 104–0045 Tokyo, Japan
E-mail: knishio@gan2.res.ncc.go.jp
Tel.: +81-3-35422511
Fax: +81-3-35475185

T. Shimoyama · Y. Fujiwara · T. Tamura · N. Saijo
Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

K. Nishio (✉) · T. Arao
Pharmacology Division,
National Cancer Center Research Institute, Tokyo, Japan

Correlative studies at the National Cancer Center Hospital

Molecular correlative studies are essential for the development of anticancer molecular-targeted drugs. One of the major purposes of a correlative study is "proof of principle" (POP). However, clinical POP studies for small molecules are often more difficult to complete than those for antibodies.

Since 2001, the National Cancer Center Hospital (Tokyo, Japan) has been operating as a laboratory for translational studies to develop molecular correlative studies. The laboratory members include medical oncologists, basic researchers, CRC research fellows, invited researchers from abroad, technicians and statisticians. The laboratory is located next to the phase I wards in the hospital, enabling more than ten molecular correlative studies to be simultaneously performed. New clinical samples can be quickly obtained from patients (including outpatients), prepared for storage and stored in the laboratory. The medical doctors

Table 1 Classification of biomarkers and their goals

Biomarker	Goal
Diagnostic markers	
Prognostic markers	
Predictive markers (patient selection)	Selection of patients most likely to benefit from given treatment
Pharmacodynamic markers	Dose finding and schedule
Response and efficacy markers	To measure or infer patient benefit/relate patient benefit to target inhibition
Toxicity prediction markers	

working in the laboratory are often research fellows supported by government grants as these individuals are often interested in this kind of research.

The location of the laboratory also gives frequent opportunities to medical oncologists to communicate with researchers. The significance of study endpoints, study design, technical and statistical information and feasibility are often discussed, especially among young medical oncologists and researchers. As a result, young oncologists and researchers often collaborate in the proposal of new molecular correlative studies.

The major activities of the laboratory are pharmacokinetics and pharmacodynamics studies for early clinical trials (phase I–II) and reverse translational studies. Essentially, "biomarker monitoring" using various biological technologies in these clinical studies are preformed. The selection and validation of biomarkers is a major endpoint for molecular correlative studies. Biomarkers are defined as described in Table 1. Tissue banking and quality control are two of the most important activities. Part of clinical sample testing is performed in collaboration with the Contract Research Organization (CRO) (Fig. 1).

Gene expression profiles

Gene expression array (DNA chips) has been widely used in clinical studies to predict response and in POP studies [3]. Many kinds of DNA chip are now available. Oligonucleotide arrays containing > 40,000 genes have recently become popular. These chips can be used differentially depending on the requirements. Before the clinical use, however, an array's quality (linearity and reproducibility) should be determined in preclinical studies. At the National Cancer Center Hospital, the quality of each array is evaluated and expressed as the Pearson's product-moment coefficient of correlation. Based on the validated quality of the cDNA, protocols based on "experienced designs" are then established.

In clinical settings, sample quality and protocol feasibility are often major limitations in the design of new studies. To maintain the quality of clinical samples, a system for sample flow has been established. First, purity of the nucleotides must be carefully examined. Purification methods largely depend on the tumor types. For example, brain tumors contain large amounts of carbohydrate chains, lung cancer samples are sometimes very hard, and breast cancer biopsy samples are lipid rich. These sample characteristics influence the purification quality and efficiency.

After the gene expression profiles have been obtained for each sample, the data are analyzed by standardization, clustering, statistical analysis and validation methods. Statistical and biological validation are essential. Ideally, clinical cross-validation studies should be performed for independent clinical studies. On the other

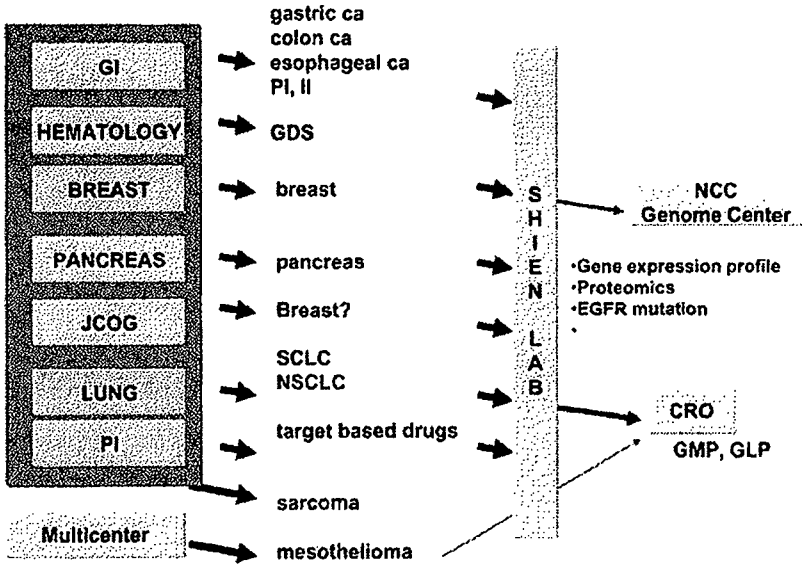


Fig. 1 Flow of clinical samples in molecular correlative studies at the National Cancer Center Hospital. (*GI* gastrointestinal, *JCOG* Japan Clinical Oncology Group, *PI* clinical phase I study, *PII* clinical phase II study, *GDS* gene delivery system, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *NCC* National Cancer Center, *CRO* Contact Research Organization, *GMP* Good Manufacturing Practice)

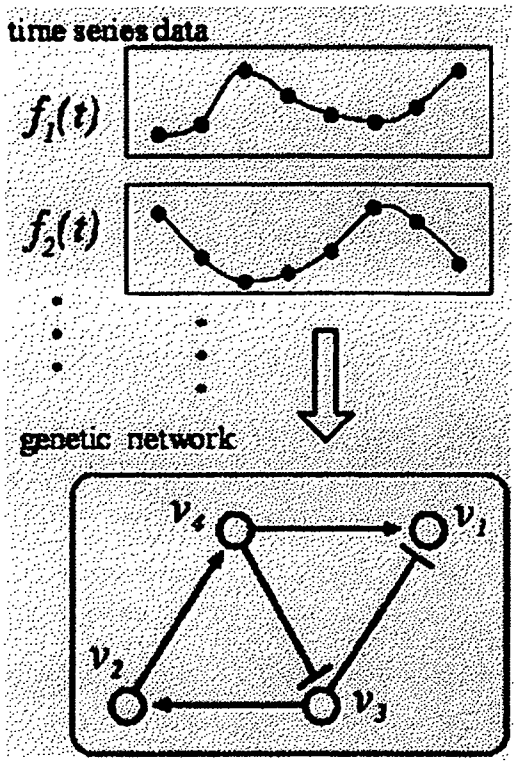


Fig. 2 Network analysis to determine transcriptional pathway and signal transduction pathway modulated by transcriptional regulators and multitarget tyrosine kinase inhibitors using gene expression profiling dataset

hand, biomarkers can be validated in the same clinical study by the "leave-one-out" method. The endpoint of these correlative studies is usually the selection of biomarkers for predicting response or toxicity. For such endpoints, the quality of the clinical study itself is also very important.

We have also used other endpoints in early clinical studies, such as comparing clinical samples obtained before and after the treatment. Analysis of gene alterations after treatment can be utilized to reveal pharmacodynamic effects. We have completed such correlative studies as part of a clinical assessment of multitarget tyrosine kinase inhibitors (TKI), farnesyl transferase inhibitor, and cytotoxic drugs [7].

For biological confirmation, we usually perform real-time RT-PCR and immunostaining. However, we recently discovered that "pathway analysis" is a powerful method for improving our understanding of the alteration of genes related to biological signal transduction pathways. To analyze transcription factors, "network analysis" can be used to identify their signaling pathways (Fig. 2).

Toxicogenomic project for breast cancer

As an approach of gene expression profiling in clinical samples, we monitored gene expression in breast cancer

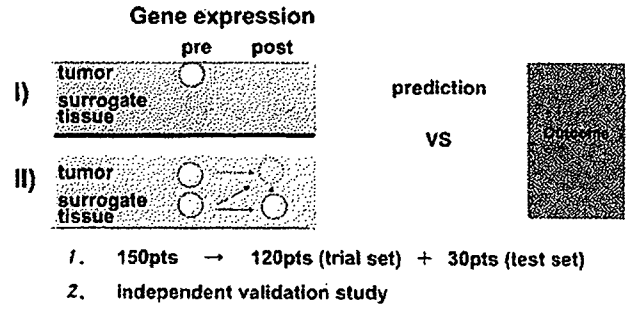


Fig. 3 Gene expression monitoring to distinguish the outcome of treatment for breast cancer patients

patients during treatment with FEC followed by weekly paclitaxel ± trastuzumab in the adjuvant setting. The purpose of this approach was to predict outcomes as well as to study the pharmacodynamic effects of each treatment. Gene expression profiles of peripheral blood mononuclear cells obtained pre- and posttreatment and of tumor biopsy samples obtained pretreatment were determined (Fig. 3). An algorithm to distinguish outcomes using the dataset of these three sampling points was created and expected to be more powerful than conventional outcome assessment techniques.

It seems quite an unusual approach to use normal cells in gene expression profiling in oncology; however, this has proved to be a useful way to monitor drug pharmacodynamic effects and to select biomarkers. Using this approach, we selected biomarkers to capture adverse effects of the treatments. Such "biomarker monitoring" is a rapidly growing field of research.

Biomarker monitoring for tyrosine kinase inhibitors

Recently, EGFR mutation has become an exciting topic in research on TKI [4, 6]. Mutation analysis is now essential for any correlative studies for TKI. Patients with tumors containing the EGFR mutation in different exons are thought to have different responses to TKI. A short, in-frame deletional mutant (E746-A750del) is one of the major mutant forms of EGFR in Japanese populations, and a determinant for EGFR-specific TKI such as gefitinib and ZD6474 (Fig. 4) [1, 8]. We investigated the biological and pharmacological functions of this mutated EGFR to determine whether tumors with deletional-EGFR status are responsive to ligand stimulation, whether mutated EGFR is constitutively active, and whether the downstream intracellular signaling pathway is altered. We concluded that deletional EGFR is constitutively active and that its downstream events are shifted to the AKT pathway (Fig. 5). In addition, a cell-free kinetic assay using mutant EGFR proteins demonstrated differential affinity to TKI among different EGFR mutants. Additional mutations after treatment are also generating interest with regard to their role in acquired resistance to TKI [2]. Thus, the mutation

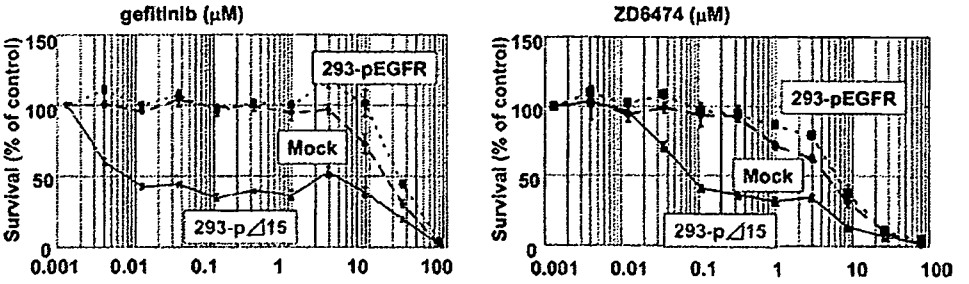
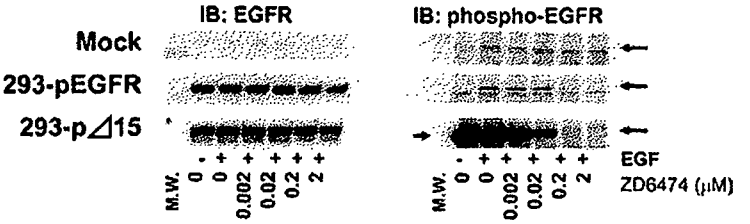


Fig. 4 In vitro sensitivity of 293 cells transfected with a deletional epidermal growth factor receptor (*EGFR*) gene (E746-A750) to tyrosine kinase inhibitors (gefitinib and ZD6474) determined by MTT assay. EGFR mutation (E746-A750 type deletion) increases sensitivity to tyrosine kinase inhibitors (gefitinib and ZD6474). HEK293 cells were transfected with empty vector (293-mock), wild-type EGFR (293 p-EGFR), and deletional EGFR (293-pΔ15). Reprinted with permission of the American Association for Cancer Research Inc., from Arao et al. [1]



Simple Δ15 *vs* Del L747-P753insS ?

Fig. 5 Constitutive phosphorylation of mutant EGFR. Phosphorylation of EGFR was determined by immunoblotting in 293 cells transfected with Mock, wild-type EGFR, and deletional EGFR cDNA. Increased phosphorylation was observed in the 293-pΔ15 cells under no ligand stimulation. Reprinted with permission of the American Association for Cancer Research Inc., from Arao et al. [1]. (*EGF* epidermal growth factor receptor, *IB* immunoblotting)

status of EGFR is one of the determinants for the prediction of tumor response to EGFR-targeted TKI. On the other hand, the clinical impact of EGFR mutation on survival in patients treated with these TKI remains unclear. Therefore, molecular correlative study including EGFR mutation analysis is quite important for prospective studies. Various technologies for EGFR mutation assay have been developed and some of these assays have been validated in the clinical situation [5]. Gene mutation analysis in prospective studies of TKI using standardized technologies is very important.

Protein arrays

Proteomics technology has been developed and successfully used to identify biomarkers for target-based drugs in a few clinical studies. Additional approaches such as antibody arrays and "PowerBlots®", especially those using phospho-specific antibodies, should enable us to perform "kinome" analyses. Hence, these protein analysis technologies are now powerful tools for research on TKI.

Acknowledgements This work was supported by funds for the Third Term Comprehensive 10-Year Strategy for Cancer Control and a Grant-in-Aid for Scientific Research and for Health and Labour Science Research Grants, Research on Advanced Medical Technology, H14-Toxico-007.

References

1. Arao T, Fukumoto H, Takeda M, Tamura T, Saijo N, Nishio K (2004) Small in-frame deletion in the epidermal growth factor receptor as a target for ZD6474. Cancer Res 64:9101–9104
2. Koizumi F, Shimoyama T, Taguchi F, Saijo N, Nishio K (2005) Establishment of a human non-small cell lung cancer cell line resistant to gefitinib. Int J Cancer 116:36–44
3. Korfee S, Eberhardt W, Fujiwara Y, Nishio K (2005) The role of DNA-microarray in translational cancer research. Curr Pharmacogenomics (in press)
4. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139
5. Nishio M, Ohyanagi F, Horiike A, Ishikawa Y, Satoh Y, Okumura S, Nakagawa K, Nishio K, Horai T (2005) Gefitinib treatment affects androgen levels in non-small-cell lung cancer patients. Br J Cancer 92:1877–1880
6. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304:1497–1500
7. Shimoyama T, Yamamoto N, Hamano T, Tamura T, Nishio K (2005) Gene expression analysis to identify the pharmacodynamic effects of docetaxel on the Rho signal pathway in human lung cancer patients (abstract 2002). Proc Am Soc Clin Oncol 23:135s
8. Taguchi F, Koh Y, Koizumi F, Tamura T, Saijo N, Nishio K (2004) Anticancer effects of ZD6474, a VEGF receptor tyrosine kinase inhibitor, in gefitinib ("Iressa")-sensitive and resistant xenograft models. Cancer Sci 95:984–989

Unusual Late Pulmonary Complication in a Child After Umbilical Cord Blood Transplantation

High-Resolution CT—Pathologic Correlation

Masahiro Endo, MD, Hiroyoshi Furukawa, MD,* Takeshi Aramaki, MD,* Naoki Morimoto, MD,* Takayoshi Uematsu, MD,* Seigo Yukisawa, MD,* Sachiko Yuen, MD,* Nobuyuki Yamamoto, MD,† Yasuhisa Ohde, MD,‡ Haruhiko Kondo, MD,‡ and Koji Amano, MD§*

Abstract: We encountered a late pulmonary complication after umbilical cord blood transplantation (UCBT) that has not been previously reported. High-resolution CT (HRCT) findings of this disease were compared with the pathology. HRCT obtained on inspiration showed dilated thick-walled bronchioli, and innumerable centrilobular linear and branching structures in the bilateral middle and lower lobes. Neither mosaic perfusion nor air-trapping was seen in HRCT on inspiration and expiration. These HRCT findings were atypical compared with those of former bronchiolitis obliterans (BO) after bone marrow transplant (BMT). Pathologic specimens obtained by open lung biopsy showed thickening of the wall from the distal bronchioli to the alveolar ducts due to submucosal and intraepithelial infiltration of lymphocytes, histiocytes and foamy macrophages, which was not accompanied by organizing changes. These changes resemble lymphocytic bronchiolitis in lung transplant recipients, which was well correlated with HRCT findings. We think that our case was a new late pulmonary complication after UCBT.

Key Words: high-resolution CT, umbilical cord blood transplantation, lung complication, bronchiolitis, chronic graft-versus-host disease

(*J Thorac Imaging* 2005;20:103–106)

A wide variety of pulmonary complications occur in BMT recipients and are a major cause of morbidity and death.[1] Bronchiolitis obliterans and bronchiolitis obliterans with organizing pneumonia (BOOP) are known as fatal chronic graft-versus-host diseases (GVHD) occurring more than 100 days after BMT. Umbilical cord blood transplantation (UCBT) has been recently introduced as an alternative procedure instead of conventional BMT for patients with leukemia or lymphoma because HLA-matched bone marrow donors are insufficient.[2–4] High- resolution computed tomography (HRCT) is excellent in the detection of pulmonary abnormalities.[5] Several cases have been reported of obstructive lung disease after BMT evaluated by HRCT.[6,7] However, we could not find any reports of the HRCT appearance of lung disease after UCBT. Herein, we describe a case of late pulmonary complication after allogeneic UCBT in a child that focuses on the HRCT appearance and associated pathologic findings.

CASE REPORT

A 16-year-old girl was admitted to the children's hospital in July 2001 to receive induction full-dose chemotherapy for acute myelogenous leukemia (AML, M6), but did not achieve complete remission. In October 2001, after the preparative treatment consisting of total body irradiation, thiotepa, and cyclophosphamide (CsA), she received an umbilical cord blood unit from a male donor, and they were serologically one-antigen mismatched. CsA and short-term methotrexate were administered for the prevention of acute GVHD. Although the patient had evidence of grade II acute GVHD of the skin, hemorrhagic cystitis, and cytomegalovirus infection, she was discharged in May 2002.

When the patient was admitted to our hospital to receive treatment of chronic GVHD, cyclosporin A and low-dose predonisolone (PSL) were administered. However, she had signs and symptoms of patchy skin depigmentation, dryness of the eyes, anorexia, and diarrhea. She had a slight cough but no dyspnea. Since her symptoms had been deteriorating, she was admitted to the division of pediatrics of our hospital to examine whether the chronic GVHD had worsened.

On physical examination, the patient was pale and edematous. She had no fever, normal breathing, and a respiratory rate of approximately 12 breaths per minute. Breath sounds were normal on chest auscultation. A lung function test showed a pattern of restrictive lung disease and no obstructive pattern; the forced vital capacity (FVC) was 1.67 L, the forced expiratory volume in one second (FEV1.0) was 1.39 L, and FEV1.0/FVC was 83.2%.

Chest radiography on admission (Fig. 1) showed a bilateral hyperinflation and reticulonodular opacities. HRCT on inspiration showed dilated thick-walled bronchioli, and innumerable centrilobular linear and branching structures in the right middle and bilateral lower lobes (Fig. 2A,B). However, mosaic perfusion or air-trapping were not seen in HRCT on inspiration and expiration (Fig. 3A,B). We speculated that these HRCT findings were atypical compared with those of BO after BMT, and diffuse panbronchiolitis (DPB) was also considered in the differential diagnosis.

From the *Division of Diagnostic Radiology, Shizuoka Cancer Center; †Division of Pulmonary Oncology, Shizuoka Cancer Center; ‡Division of Thoracic Surgery, Shizuoka Cancer Center; and §Division of Pediatrics, Shizuoka Cancer Center.

This case was presented at the 2004 annual meeting of the Japanese Society of Thoracic Radiology.

Reprints: Masahiro Endo, MD, Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777 Japan (e-mail: m.endo@scchr.jp).

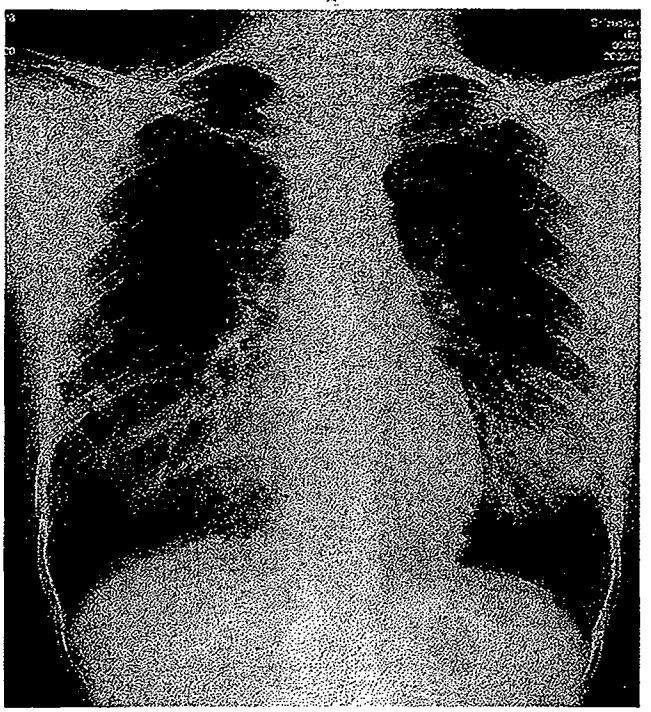


FIGURE 1. Admission chest radiograph shows bilateral hyperinflation and reticulonodular opacities that are predominantly hilar in distribution.

The patient received central intravenous nutrition and was administered an increased dose of CsA. After receiving the treatment, general conditions and laboratory data gradually improved. With the recovery of the gastrointestinal symptoms, her cough was decreasing but the chest radiographic findings were unchanged. Her clinical course, lung function test, and radiologic imaging were not compatible with BO after BMT. To determine the nature of her lung disease, open biopsy of the right middle lobe (segment 4b) and lower lobe (segment 8b) using video-associated thoracoscopy was performed with informed consent of the patient and parents. The laboratory data at the operation are shown in Table 1.

Pathologic specimens showed thickening of the wall of distal bronchioli due to submucosal and intraepithelial infiltration of lymphocytes and plasma cells (Fig. 4A,B). Foamy macrophages were also observed in the alveoli near thickened bronchioli. No organizing changes such as intraluminal fibrosis were seen. These findings were more conspicuous in segment 4b than in segment 8b. There was no evidence of bacterial or fungal infection. Therefore, the final pathologic diagnosis was bronchiolitis without organizing changes resembling lymphocytic bronchiolitis. After the administration of an increased dose of PSL, the cough and the HRCT findings were apparently improved (Fig. 5A,B).

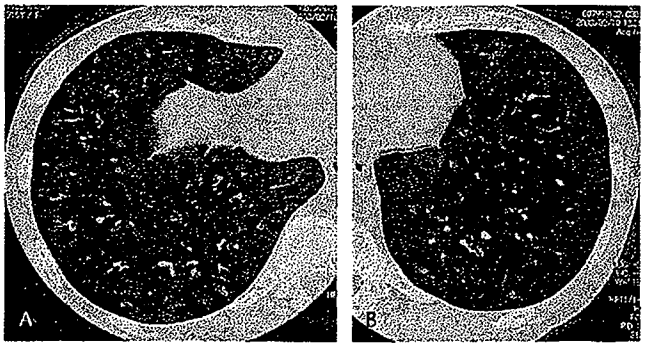


FIGURE 2. HRCT scan (1 mm collimation with high-resolution algorithm) on inspiration shows dilated thick-walled bronchioli, and innumerable centrilobular linear and branching structures in the right middle and bilateral lower lobes.

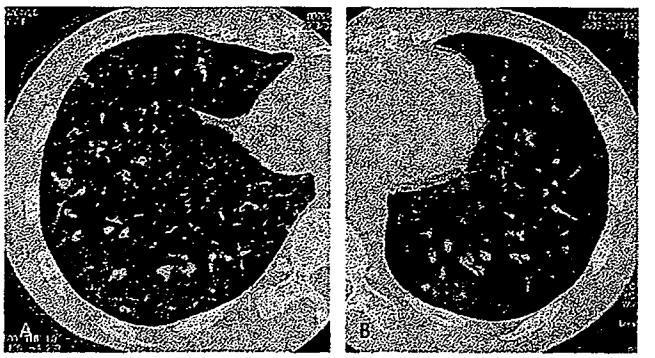


FIGURE 3. Mosaic perfusion or air-trapping are not seen in HRCT scan on expiration.

DISCUSSION

Chronic GVHD resembles an autoimmune disorder occurring 100 days after allogeneic transplantation and occurs in approximately 60–80% of long-term survivors of allogeneic hematopoietic cell transplant.[1] This immunologic complication is a major cause of morbidity and mortality, accounting for about one-quarter of the deaths in long-term survivors of transplants. Clinical manifestations of chronic GVHD are similar to autoimmune collagen vascular diseases, such as oral ulcerations, keratoconjunctivitis sicca, xerostomia, intrahepatic obstructive liver disease, and obstructive pulmonary disease. Our patient had many of these clinical manifestations.

Obstructive pulmonary disease after BMT was first reported in 1982.[8] BO occurs in up to 10% of BMT recipients but rarely after autologous transplantation. The clinical cause is uncertain but it considered the same as that of chronic GVHD. Some pathogenic mechanisms of fatal obstructive lung disease have been reported. Yousem proposed that GVHD insults to the lung might lead to a pattern of pulmonary scarring that is localized in the airways and perivascular zones.[9] On the other hand, Muller et al described that the primary pathologic process is an activated host immune response to the presence of viral antigen in the lung.[10] Usually, symptoms such as cough appear at 3 to 20 months after BMT and then progress to dyspnea, progressive airflow obstruction, and finally to respiratory failure. They respond poorly to corticosteroids and other immunosuppressive therapy and progress over months to years to become oxygen-dependent, culminating in respiratory failure. An obstructive pattern of pulmonary function tests, typical symptoms, and no evidence of infection are regarded as diagnostic of BO after BMT.

While it is considered that chest radiography of BO is usually normal but sometimes shows hyperinflation,[5] our case

TABLE 1. Laboratory Data at the Operation

WBC	5900/μL
RBC	314 10^4/μL
HB	10.8 g/dL
PLT	6.1 10^4/μL
CRP	0.05 mg/dL
ALB	3.5 g/dL
GOT	22 IU/dL
GPT	17 IU/dL
LDH	206 IU/dL
PaO2	99.3 torr
PaCO2	34.7 torr
PH	7.387
BE	−3.8
HCO3−	20.4

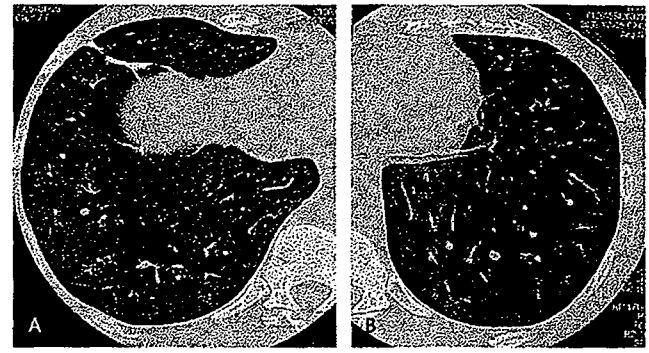


FIGURE 5. HRCT scan (1 mm collimation with high-resolution algorithm after the therapy demonstrates improved dilated thick-walled bronchioli and the centrilobular linear and branching opacities.

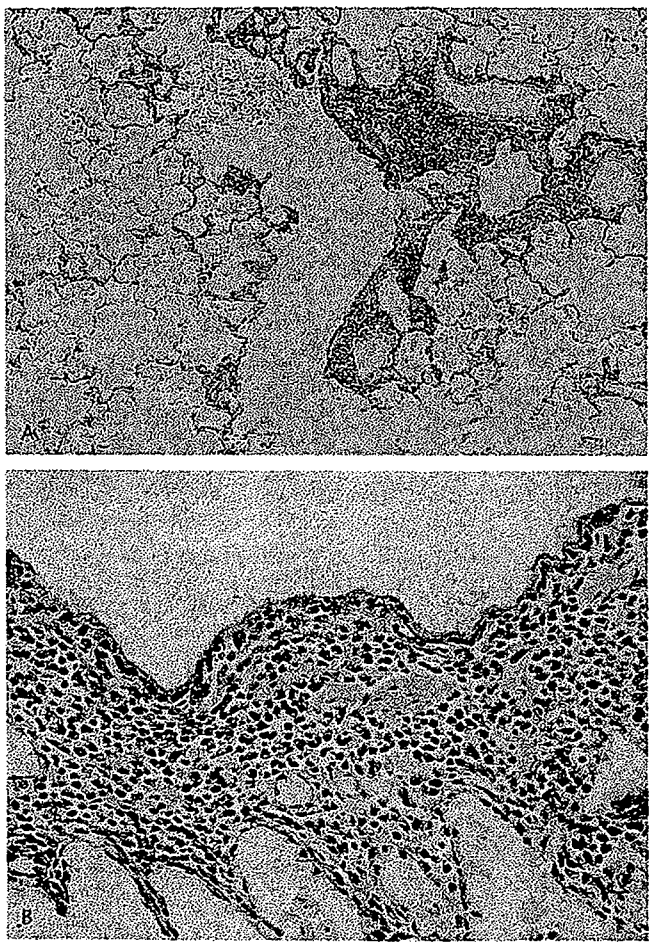


FIGURE 4. A, Photomicrography (hematoxylin and cosin, original magnification (×4) demonstrates a thickened wall of the distal bronchioli. B, Infiltrations of lymphocytes and plasma cells are seen in submucosal and intraepithelial lesion of the thickened bronchial wall (hematoxylin and cosin, original magnification (×40). Foamy macrophages were also involved in the alveoli near thickened bronchioli.

showed mild hyperinflation. HRCT is used for differential diagnosis of pulmonary complications after BMT.[6,7] Typical HRCT findings of BO after BMT are bronchial dilatation, a mosaic pattern of attenuation, and air trapping on expiratory scans.[5] Sargent et al reported that bronchial dilatation was more common in subsegmental than in segmental bronchi.[6] Ooi et al reported that normal, nonspecific bronchial dilatation and consolidation were typical findings of BO after BMT on HRCT,[11] although these findings were not specific. Histologically, there is predominantly constrictive bronchiolitis with a prebronchiolar inflammatory infiltrate of neutrophils and lymphocytes, which accounts for the air trapping seen on the expiratory CT scan.[5] In our case, HRCT suggested that the typical pathologic findings of BO and BOOP after BMT were not present.

We considered the final pathologic diagnosis of this case to be bronchiolitis without organizing changes resembling lymphocytic bronchiolitis. The pathologic changes mainly occurred in the periphery and there were more infiltrated macrophages, compared with BO after BMT. Furthermore, the presence of foamy macrophages and more peripheral bronchiolitis was similar to the pathology of DPB, but centrilobular peribronchiolar acute and chronic inflammatory cells and intraluminal inflammatory exudates, which are typical findings of DPB, were not present. The International Society of Heart-Lung Transplantation has revised a working formulation for the classification and grading of pulmonary rejection,[12,13] in which lymphocytic bronchiolitis is listed as airway inflammation. It is manifested by a patchy or diffuse submucosal infiltrate of lymphocytes and plasma cells.[14] Also, it has been reported that it may accompany or succeed the perivascular infiltrates of early rejection or be seen alone, and often responds to steroid treatment.[15] Based on the literature and the pathology, we decided that our patient had a new type of late pulmonary complication and the pathology was a variation of lymphocytic bronchiolitis. Thus, the corticosteroid treatment improved her clinical symptoms and radiographic appearances. Consequently, the HRCT findings were different from those of typical BO, and did not demonstrate an obstructive pattern.

GVHD occurs infrequently in patients after UCBT because the proliferative and cytotoxic responses of cord blood lymphocytes are blunted compared with those of adult peripheral lymphocytes.[3] However, our case had grade 2 chronic GVHD including lung complication. A case of fatal obstructive lung disease with severe GVHD after UCBT has been reported,[16] in which it was proposed that more investigation would be needed to analyze the degree of HLA disparities that is tolerable in UCBT. In our case, one antigen was mismatched since the pulmonary complications were progressive and the patient's condition was often not tolerable; open lung biopsy in bone marrow transplant patients is usually not attempted and it has been reported that it may not improve patient outcome, while histopathologic analysis is easy and accurate in determining the cause of pulmonary infiltrates.[17] We obtained open lung biopsy specimens, analyzed the histopathologic manifestations, and compared them to HRCT findings. While several types of HRCT findings on pulmonary complications after BMT have been reported, we think this is the first report of HRCT findings on this new type of pulmonary complication after UCBT. As it is speculated that the transplantation of umbilical cord blood may be a cause of developing a pulmonary complication such as ours, more investigations will be needed.

In conclusion, we experienced a new type of late pulmonary complication after UCBT and compared the HRCT findings and the pathology. This new type of late lung complication may occur more often with the increased frequency of UCBT.

ACKNOWLEDGMENT

The authors thank Dr. Ichiro Yamadori of the National Okayama Medical Center for reviewing the open lung biopsy specimens.

REFERENCES

1. Ratanatharathorn V, Ayash L, Lazarus HM, et al. Chronic graft-versus-host disease: clinical manifestation and therapy. *Bone Marrow Transplant.* 2001;28:121–129.
2. Wagner JE, Kernan NA, Steinbuch M, et al. Allogenic sibling umbilical cord blood transplantation in children with malignant and non-malignant disease. *Lancet.* 1995;346:214–219.
3. Moretta A, Maccario R, Fagioli F, et al. Analysis of immune reconstitution in children undergoing cord blood transplantation. *Exp Hematol.* 2001;29: 371–379.
4. Yoshimatsu T, Manabe A, Tanaka R, et al. Successful treatment of relapsed blastic natural killer cell lymphoma with unrelated cord blood transplantation. *Bone Marrow Transplant.* 2002;30:41–44.
5. Webb WR, Mueller NL, Naidich DP. High-resolution CT of the Lung. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
6. Sargent MA, Cairns RA, Murdoch MJ, et al. Obstructive lung disease in children after allogeneic bone marrow transplantation: evaluation with high-resolution CT. *Am J Roentgenol.* 1995;164:693–696.
7. Worthy SA, Flint JD, Mueller NL. Pulmonary complications after bone marrow transplantation: high-resolution CT and pathologic findings. *Radiographics.* 1997;17:1359–1371.
8. Roca J, Granena A, Rodriguez-Roisin J, et al. Fatal airway disease in an adult with chronic graft-versus-host disease. *Thorax.* 1982;37:77–78.
9. Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. *Hum Pathol.* 1995;26: 668–675.
10. Muller CA, Hebart H, Roos A, et al. Correlation of interstitial pneumonia with human cytomegalovirus-induced lung infection and graft-versus-host disease after bone marrow transplantation. *Med Microbiol Immunol (Berl).* 1995;184:115–121.
11. Ooi GC, Peh WC, Ip M. High-resolution computed tomography of bronchiolitis obliterans syndrome after bone marrow transplantation. *Respiration (Herrlisheim).* 1998;65:187–191.
12. Yousem SA, Berry GJ, Brunt EM, et al. A working formulation for the standardization of nomenclature in the diagnosis of the heart and lung rejection: Lung Rejection Study Group. *J Heart Transplant.* 1990;9:593–601.
13. Yousem SA, Berry GR, Cagle PT, et al. Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group. *J Heart Lung Transplant.* 1996;15:11–15.
14. Yousem SA. Lymphocytic bronchitis/bronchiolitis in lung allograft recipients. *Am J Surg Pathol.* 1993;17:491–496.
15. Corrin B. Lung transplantation. In: Corrin B, eds. *Pathology of the lungs.* London: Churchill Livingstone; 2000:447–454.
16. Ohnuma K, Toyoda Y, Ishida Y, et al. Fatal obstruction lung disease after haploidential sibling cord blood transplantation. *Bone Marrow Transplant.* 1998;21:939–941.
17. Hayes-Jordan A, Benaim E, Richardson S, et al. Open lung biopsy in pediatric bone marrow transplant patients. *J Pediatr Surg.* 2002;37:446–452.

www.nature.com/clinicalpractice/onc

What phase III trials are needed to improve the treatment of advanced non-small-cell lung cancer?

Nagahiro Saijo

Platinum-based doublets are standard treatments for stage IV non-small-cell lung cancer (NSCLC). Several doublets that include new drugs improve survival, but no one regimen is clearly superior to the others, as previously discussed by Scagliotti[1] and Govindan[2] in *Nature Clinical Practice Oncology*.

Numerous molecular-target-based drugs have been introduced for the treatment of NSCLC, but can they replace or be used as an adjuvant to current therapy, and can they be combined with other chemotherapeutic agents, radiotherapy and/or surgery? We hypothesize that incorporation of novel molecular-target-based therapies into current treatment paradigms will improve outcomes. However, carefully designed clinical trials and translational science will be required to identify the subsets of patients likely to benefit. If these treatment strategies are to be used, we must first answer the following critical questions. First, will patients lacking the target still respond? It is still unclear why responses occur in those lacking the correct molecular target. Second, what expression levels of the target are sufficient for a response, and can we measure the target in a biologically relevant and/or technologically valid way? Third, does the agent inhibit the proposed target at the dose and schedule utilized? Fourth, is the target a critical driving force for cell growth in the tumor type in question?

Various molecular-target-based drugs for advanced NSCLC have been evaluated in randomized controlled trials, but the majority, including a matrix metalloproteinase inhibitor, a protein kinase C inhibitor, and trastuzumab, have yielded negative results.[3,4] Gefitinib (Iressa®) and erlotinib (Tarceva™) are orally available selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) that exhibit antitumor activity in patients with previously treated advanced NSCLC. However, both drugs failed to show additive or synergistic effects when combined with platinum-based chemotherapy as a first-line treatment for NSCLC. On 17 December 2004, AstraZeneca announced the preliminary results of their ISEL (Iressa® Survival Evaluation in Lung Cancer) study of 1,692 patients with advanced recurrent or refractory NSCLC. Unfortunately, gefitinib failed to prolong survival significantly compared with placebo (hazard ratio 0.89, $P=0.11$) in the overall patient population or among patients with adenocarcinoma (hazard ratio 0.83, $P=0.07$). A retrospective analysis of patients treated with gefitinib showed that tumor response was associated with distinct subgroups: women, patients with no history of smoking, patients with adenocarcinoma, and Japanese patients. Survival in the gefitinib group in the ISEL study was significantly higher for non-smokers ($P<0.01$) and Asians ($P<0.01$) than in the placebo group. The survival curves of the two treatment groups were the same for non-Asians. The results of similar randomized trials of erlotinib (the BR21 study) were presented at the American Society of Clinical Oncology meeting in 2004. Erlotinib significantly prolonged survival in patients with advanced, previously treated, refractory or recurrent NSCLC. The survival of non-smokers in the erlotinib group in the BR21 study was extremely good and contributed to the improvement in overall survival. The presence of an *EGFR* mutation has been demonstrated to be a strong predictor of a favorable response to EGFR-TKI. Mutations have recently been reported to be significantly more frequent in women, in patients with adenocarcinoma, and in those who had never smoked, and these findings are consistent with the clinical predictors of tumor response in patients treated with EGFR-TKI. Mitsudomi *et al.* reported that patients with *EGFR* mutations survived longer after the initiation of gefitinib treatment than those without mutations.[5] It can be concluded that translational studies are extremely important for the development of molecular-target-based drugs.

Supplementary information, in the form of a reference list, is available on the *Nature Clinical Practice Oncology* website.

Numerous molecular-target-based drugs have been introduced for the treatment of NSCLC, but what is their place in current therapy?

N Saijo is an Advisory Board member of Nature Clinical Practice Oncology.

Competing interests
The author declared he has no competing interests.

www.nature.com/clinicalpractice
doi:10.1038/ncponc0199

わが国の大規模臨床試験FACSの成績から

大江裕一郎
国立がんセンター中央病院肺内科

はじめに

遠隔転移もしくは胸水・心嚢水などを有する非小細胞肺癌に対する標準的治療は化学療法であり，プラチナ製剤と1990年代に開発された第3世代抗癌薬との2剤併用が標準的な化学療法レジメンと考えられている。しかし，プラチナ製剤と第3世代抗癌薬の2剤併用同士の比較では大きな差は認められず，毒性の違いを勘案して化学療法レジメンを選択することが推奨されている。

欧米では1990年代後半までにプラチナ製剤と第3世代抗癌薬の2剤併用療法同士を比較する第III相試験が数多く実施されている[1~4]。一方，わが国ではイリノテカン，ドセタキセルは比較的早い時期に市販されたものの，パクリタキセル，ゲムシタビン，ビノレルビンの非小細胞癌に対する承認が得られたのは1999年になってからである。わが国で抗悪性腫瘍薬は第II相試験の結果に基づいて承認され，市販後に第III相試験を実施することが製薬企業に課せられている。欧米に遅れること数年，1999年のほぼ同時期にようやく非小細胞癌に対する上記の標準的治療薬3剤が承認され，これらの第III相試験を実施することが必要となった。しかし，ほぼ同時に非小細胞癌を対象に第III相試験を3つも実施することは不可能であり，無理に実施したとしても臨床試験の質に問題が生じることが強く懸念された。そこで製薬企業3社と研究者サイドが協議の結果，4群の第III相試験(FACS: Four-Arm Cooperative Study)が実施された[5]。

FACSの概要

FACSではIV期もしくは胸水などを有するIIIB期の非小細胞癌を対象に，図1に示す用法・用量でシスプラチン＋イリノテカン(IP)を標準治療として，この試験の試験治療であるカルボプラチン＋パクリタキセル(TC)，シスプラチン＋ゲムシタビン(GP)，シスプラチン＋ビノレルビン(NP)を比較した。わが国で開発されたイリノテカンが標準治療として採用されているが，FACSはイリノテカンを含む治療をプラチナ製剤と第3世代抗癌薬の併用と比較した唯一の第III相試験である。

主要エンドポイントは生存とし，標準治療であるIPに対して，TC，GP，NPがそれぞれ1年生存率で10%以上劣らないことを証明する非劣性試験のデザインで試験が実施された。当初の登録予定期間は3年であったが，登録が順調に進み，2000年10月から2002年6月に合計602例が全国の44施設より登録された。登録された602例中，592例で毒性の評価が可能であり，有効性の評価が可能であった症例は581例であった(表1)。

有効性の結果は表2のとおりであった。奏効率，生存期間，無

図1 FACSの試験デザイン[5]

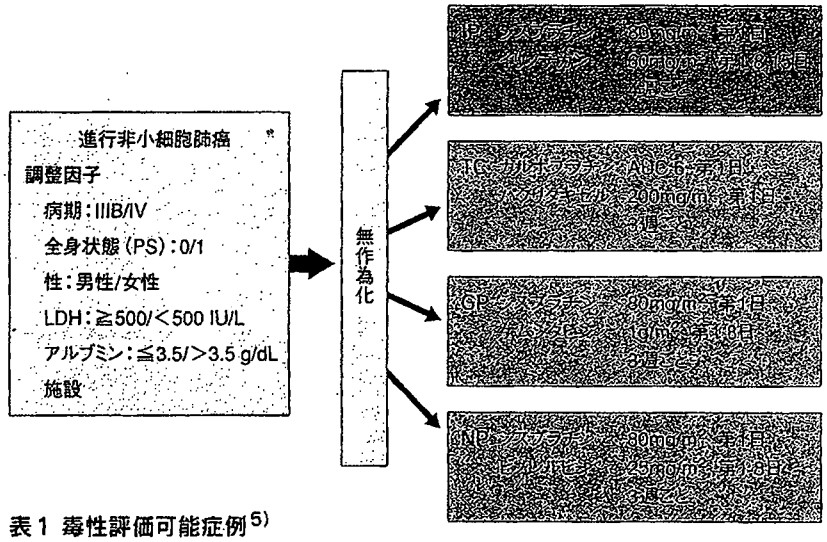


表1 毒性評価可能症例[5]

	IP	TC	GP	NP
毒性評価可能症例数	147	148	151	146
性(男性/女性)	99/48	102/46	103/48	102/44
年齢中央値(範囲)	62(30～74)	63(33～74)	61(34～74)	61(28～74)
全身状態：PS(0/1)	45/102	45/103	48/103	46/100
病期(IIIB/IV)	32/115	29/118	31/118	26/110
組織* Ad	122	107	109	110
Sq	16	31	31	29
その他	9	10	9	7
LDH(IU/L)：≧500/＜500	19/128	22/126	21/130	18/128
アルブミン(g/dL)：≦3.5/＞3.5	39/108	35/113	34/117	38/108

*χ^2検定により，TCとIPの比較で$p<0.05$