The reasons for this difference in incidence of ILD between Japan and other countries remain unclear, but may relate to both constitutional and environmental factors specific to Japan or Japanese patients.

Regulatory affairs

Gefitinib is approved in 36 countries worldwide for the treatment of NSCLC (Box 1). Gefitinib was approved for clinical use in Japan on 5 July 2002, ahead of many countries in the world. It was approved by the FDA on 5 May 2003 and, subsequently, by several other countries. However, in the wake of the aforementioned ISEL trials, which indicated the failure to improve survival time with gefitinib in comparison with placebo, an application for approval for gefitinib to the EMEA was withdrawn on 4 January 2005, and the FDA has restricted the labeling of gefitinib. However, an application for approval for gefitinib was subsequently submitted to the EMEA in May 2008 following reporting of the INTEREST trial.

Conclusion

Gefitinib is generally well tolerated, has encouraging efficacy and quality of life benefits and offers hope for patients with advanced lung cancer. Gefitinib is effective as a first-, second- or third-line treatment option for advanced NSCLC. Despite the failure of combining TKIs with chemotherapy in several large Phase III clinical trials, sequential dosing regimens of gefitinib with chemotherapy is still a viable clinical research paradigm (WJTOG0203). In addition, recent results of a randomized Phase III study (IPASS) have shown an improved PFS in the gefitinib arm, indicating the possibility of gefitinib as a first-line therapy in selected patients. As a second-line therapy, gefitinib has been shown to be equivalent to docetaxel in terms of OS, with less toxicity and improved quality of life. There is some evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival, although this is not always the case, as highlighted by the results of the INTEREST study. In the near future, treatments may be selected based on the results of *EGFR* and *KRAS* mutation status, *EGFR* copy number or, possibly, the type of histology (adenocarcinoma). Ongoing prospective trials in which patients with *EGFR* mutations are randomized to chemotherapy or EGFR TKI should help to determine the importance of mutation testing in selecting therapy for subsets of patients with lung cancer. In summary, gefitinib has provided an important alternative approach for palliation of previously treated advanced disease NSCLC patients, and it is likely that there will be increasing use of first-line gefitinib in subgroups of NSCLC patients based on their clinical and molecular characteristics.

Expert commentary

The use of the TKIs gefitinib and erlotinib grew substantially as agents for second- and third-line therapies, replacing a proportion of injectable chemotherapy agents. Although gefitinib has provided an important alternative approach for palliation of previously treated advanced NSCLC patients and is currently not approved for first-line use, it is likely that there will be increasing use of first-line gefitinib in subgroups of NSCLC patients based on their clinical and molecular characteristics. In prior studies, the predictive factors of gefitinib response were female gender, never-smoking status and adenocarcinoma histology. Indeed, before the emerging understanding of EGFR mutations, these factors were important references for physicians in choosing susceptible patients to gefitinib treatment. Grouping patients into best, intermediate and worst categories with respect to potential benefit from gefitinib has practical implications. Based on currently available information, an example of one of the best groups might include Asian women who have never smoked and have adenocarcinoma. An intermediate group might

Box 1. Countries where gefitinib is approved for use.

- Japan
- Australia
- USA
- Argentina
- Singapore
- South Korea
- Taiwan
- Malaysia
- Mexico
- Philippines
- Canada
- Curacao
- Dominican Republic
- Nicaragua
- Hong Kong
- Israel
- New Zealand
- Honduras
- Guatemala
- Thailand
- United Arab Emirates
- Switzerland
- Indonesia
- India
- Peru
- El Salvador
- Bahrain
- Panama
- Venezuela
- Chile
- Serbia/Montenegro
- Uruguay
- Qatar
- Russia
- China
- Sri Lanka

comprise smokers with adenocarcinoma, and the worst group might consist of male smokers with squamous cell carcinoma. However, clinicians are also faced with the question of whether gefitinib treatment is worthwhile in specific patient subgroups based on their clinical characteristics. It has been reported that gefitinib was more effective in never-smokers than smokers, but it is important to note that the risk of death was reduced even in smokers subsets [17,108]. Thus, at this point, it does not seem that patients should be excluded from gefitinib treatment based solely on clinical considerations. Perhaps, more importantly, we need to gather more information regarding the benefit of chemotherapy versus gefitinib in specific patient populations. The observation of higher response rates with gefitinib in selected groups of patients, as well as the disappointing results with simultaneous chemotherapy and gefitinib in unselected patients, led lung cancer researchers to study the potential predictive value of molecular profiles in patients treated with gefitinib. There is increasing evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival. By contrast, *KRAS* mutations may predict the worst outcomes on gefitinib. Determining the optimum way to select patients for future therapy seems to be a key factor in improving results for individual lung cancer patients.

Five-year view

Gefitinib was the most commonly prescribed EGFR TKI, and still is in Japan and Asia, but the use of gefitinib as a proportion of all second-line therapies declined rapidly during the period of observation after findings from clinical studies suggested that it did not improve survival and after the subsequent FDA labeling change. On the other hand, erlotinib prescriptions increased substantially. However, sequential dosing regimens of gefitinib with chemotherapy is a viable clinical research paradigm [17], and recent results of a randomized Phase III study (IPASS) have demonstrated improved PFS in the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. In addition, gefitinib has been shown to be equivalent to docetaxel in terms of overall survival with less toxicity and improved quality of life in the second-line therapy (INTEREST). Future research of gefitinib will include potential synergistic effects with chemotherapy using an intermittent combination in selected patients or *EGFR*-mutated patients. In addition, it is possible that, in the next 5 years, gefitinib may have a role in early-stage NSCLC as postoperative adjuvant therapy or neoadjuvant therapy. Currently, allowing for test availability and differing preferences, oncologists use mutational analysis to help them choose among possible treatments and to guide the most rational order that these therapies should be administered for individual patients. The *EGFR* mutation appears to be the most sensitive predictor of response to gefitinib. With the advances in sensitive and specific examination for the detection of *EGFR* mutation, such as high-resolution melting analysis, scorpion arms or mutant-enriched PCR, it is now possible to identify the status of *EGFR* mutation in patients, as long as histological samples are available [81,109–111]. Recently, Maheswaran *et al.* have reported the detection of mutations in EGFR of circulating lung cancer cells [112]. Molecular analysis of circulating tumor cells from the blood may offer the possibility of monitoring changes in epithelial tumor genotypes during the course of treatment. In the near future, treatments will be selected based on the results of *EGFR* and *KRAS* mutation status, *EGFR* copy number or possibly histology (adenocarcinoma vs nonadenocarcinoma). As we now know, however, resistance to gefitinib in patients with the *EGFR* mutation develop eventually. In 50% of these cases, the resistance was due to a second-site point mutation (T790M), 20% was due to *MET* gene amplification and the remainder due to unknown causes. Evaluation of the combination of gefitinib with other targeting agents, such as those that inhibit molecules in the same signalling pathway or angiogenesis inhibitors, may potentially enhance clinical outcome and reduce the emergence of resistance.

Key issues

- Gefitinib has encouraging efficacy, is generally well tolerated and has quality-of-life benefits.
- In prior studies, the predictive factors of gefitinib response were female gender, never-smoking status and adenocarcinoma histology.
- From a clinician's perspective, it would be useful to categorize patients into the best, intermediate, and worst EGF receptor (EGFR)-tyrosine kinase inhibitor treatment-outcome groups. Based on currently available information, an example of one of the best groups might include Asian women who have never smoked and have adenocarcinoma. An intermediate group might comprise of smokers with adenocarcinoma, and the worst group might consist of male smokers with squamous cell carcinoma.
- Sequential dosing regimens of gefitinib with chemotherapy is a viable clinical research paradigm, and recent results of a randomized Phase III study (IPASS) have showed improved progression-free survival in the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. In addition, gefitinib has been shown to be equivalent to docetaxel in terms of overall survival with less toxicity and improved quality of life in second-line therapy (INTEREST).
- Currently, the treatments (cytotoxic chemotherapy vs gefitinib) are selected based on the results of *EGFR* and *KRAS* gene mutation status, *EGFR* gene copy number or, possibly, the type of histology (adenocarcinoma).
- Among those, EGFR mutation appears to be most sensitive predictor of response to gefitinib. However, resistance to gefitinib develops eventually. In 50% of these cases, the resistance was due to a second-site point mutation (T790M), 20% *MET* gene amplification and the remainder unknown causes.
- Evaluation of the combination of gefitinib with other targeting agents may potentially enhance clinical outcome and reduce the emergence of resistance.

Financial & competing interests disclosure

This work is supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Information resources

- US Food and Drug Administration www.fda.gov/default.htm
- Medicine Net www.medicinenet.com/gefitinib/index.htm
- National Cancer Institute – Clinical trials www.cancer.gov/clinicaltrials
- AstraZeneca Pharmaceuticals information resource www.iressa.com

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Affiliations

- Toyoaki Hida
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
Tel.: +81 52 762 6111
Fax: +81 52 764 2963
107974@aichi-cc.jp
- Shizu Ogawa
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
- Jang Chul Park
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
- Ji Young Park
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
- Junichi Shimizu
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
- Yoshitsugu Horio
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
- Kimihide Yoshida
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

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Prognostic factors for lung cancer patients with brain metastases treated with whole brain radiotherapy.

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Sub-category: Local-Regional Therapy
Category: Lung Cancer--Local-Regional and Adjuvant Therapy
Meeting: 2008 ASCO Annual Meeting

Abstract No: 7570
Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 7570)
Author(s): N. Horiuchi, H. Okamoto, N. Hida, K. Naoki, T. Shimizu, K. Watanabe, A. Ishizaka

Abstract: **Background:** The purpose of this retrospective study was to clarify the role of whole brain radiotherapy (WBRT) in lung cancer patients with brain metastases (BM). **Methods:** Between February 1998 and October 2005, 103 consecutive lung cancer patients received WBRT for BM. The patients included 77 men and 26 women, ranging in age from 34 to 84 years with a median age of 65 years. Thirty-six of the patients had SCLC and 67 had NSCLC. Fifty-two patients had an ECOG performance status (PS) score of 0 to 2, and 51 had a PS score of 3 or 4. Seventy-nine patients (77%) had symptomatic BM, and 72 had multiple BM (70%). The mean dose of brain radiation was 38±8.3 Gy. Following radiation treatment, the median survival time (MST) for all patients was 4.0 months, and the 1-year survival rate was 14%. Multivariate analysis was performed using Cox proportional hazards model to evaluate the following: sex, age (<60 years vs. ≥60 years), histology (SCLC vs. NSCLC), PS score (0-2 vs. 3-4), number of BM (single vs. multiple), the presence or absence of neurological symptoms, the presence or absence of other metastases outside the brain, and lastly, any extracranial disease activity, including active or inactive primary lesions. **Results:** WBRT improved the neurological symptoms in 45 patients out of 75 symptomatic patients (60%). When multivariate analysis was performed, the favorable prognostic factors consisted of females (p=0.017), a PS score 0-2 (p=0.006), and extracranial disease activity including primary lesions (p=0.004). Based on these three prognostic factors, we subdivided the patients into four groups; the low-risk group had no risk factors, the mild-risk group had one, the moderate-risk group had two, and the high-risk group had three. The MST for the four subgroups was as follows: 548 days for the low-risk group, 195 days for the mild-risk group, 95 days for the moderate-risk group, and 58 days for the high-risk group. **Conclusions:** Although WBRT was an effective palliative treatment for lung cancer patients with BM, the MST for the high-risk group was somewhat disappointing. Further studies are necessary to evaluate quality of life and MST with or without WBRT for high-risk group patients with lung cancer.

Abstract Disclosures

Associated Presentation(s):

1. **Prognostic factors for lung cancer patients with brain metastases treated with whole brain radiotherapy.**
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   Category: Lung Cancer--Local-Regional and Adjuvant Therapy - Local-Regional Therapy
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Annals of Oncology Advance Access published February 16, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdp020

Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer

K. Hotta*, K. Kiura, Y. Fujiwara, N. Takigawa, I. Oze, N. Ochi, M. Tabata & M. Tanimoto

Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, Japan

Received 13 November 2008; revised 10 January 2009; accepted 13 January 2009

Background: The duration of, resources required for and cost of clinical trials could be reduced if a surrogate end point was to be used in place of survival. We assessed the extent to which the objective response rate (ORR) is predictive of mortality, how much difference in the ORR is needed to predict an obvious survival difference and what factors could affect the association between the two parameters during the first-line treatment of extensive disease (ED)-small-cell lung cancer (SCLC).

Methods: We used the ORRs and median survival times (MSTs) from 48 phase III trials of first-line chemotherapy involving 8779 randomised patients with ED-SCLC in a linear regression analysis. The MST difference was calculated as the difference in MST between the investigational and reference arms; the ORR difference was similarly defined.

Results: ORR difference between the treatment arms was modestly associated with the MST difference in the overall trials (R^2 = 0.3314). In contrast, the relationship was stronger among only trials in which prophylactic cranial irradiation was given to those having an objective response to the initial chemotherapy (R^2 = 0.6279). In this trial setting, large differences in ORR were needed to predict a survival advantage (1.2-day survival advantage per 2% increase in ORR).

Conclusions: In the first-line treatment of ED-SCLC, a favourable relationship was detected between the two parameters in the selected trial setting. Large ORR differences were needed to predict a survival benefit, clearly suggesting the need for new chemotherapeutic agents.

Key words: lung cancer, objective response, overall survival

original article

introduction

Lung cancer is a leading cause of cancer-related death, and small-cell lung cancer (SCLC) accounts for ~15% of all lung cancer cases. SCLC is clinically categorised according to the disease extent as either limited disease (LD)- or extensive disease (ED)-SCLC. The standard first line of treatment of ED-SCLC is platinum-based chemotherapy with cisplatin–etoposide or cisplatin–irinotecan [1, 2]. The outcome, however, is unsatisfactory, with a median survival time (MST) of ~1 year, indicating the need for novel anticancer agents.

In developing new agents, the most important issue is whether they prolong survival. This is usually evaluated in phase III trials, in which the primary end point is traditionally overall survival (OS). Phase III trials, however, are both expensive and time consuming. Moreover, a recent review of all North American phase III randomised trials for patients with ED-SCLC conducted from 1972 to 1990 determined that only 5 (24%) of 21 trials found a significant, but small, survival advantage, with a survival difference ranging from 0.8 to 3.0 months in the experimental arm compared with the control arm [3]. Considering these findings, early and accurate screening of the agents to be investigated in phase III trials is essential.

As spontaneous cancer regression is a rare event, assuming that tumour regression after treatment is attributable entirely to a treatment effect is reasonable. For this reason, the objective response rate [ORR; complete response (CR) rate and partial response (PR) rate] has historically been considered a clear indicator of antitumour activity and a surrogate for clinical benefit [4]. The ORR has the additional advantage of being an early clinical trial end point, generally reached within just 2–3 months of treatment initiation [5].

The duration, human resources required for and cost of clinical trials could be reduced if a surrogate end point was to be properly used in place of survival. To date, however, (i) the extent to which the OR is predictive of mortality in the first-line treatment of patients with ED-SCLC has not been fully assessed, even though an association itself between OR and OS has been reported [5]. In addition, (ii) how much time of OS increases as ORR increases in this disease has not been formally

*Correspondence to: Dr K. Hotta, Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama 700-8558, Japan. Tel: +81-86-235-7227; Fax: +81-86-232-8226; E-mail: khotta@md.okayama-u.ac.jp

evaluated. Furthermore, (iii) knowing what factors can affect the association between the ORR and OS would be of interest to generate relevant hypotheses in future studies. Here, we investigated the association between ORR and OS to address each of the above-mentioned points.

methods

search for trials

We searched for trials that had been conducted from January 1990 to August 2008, as previous reports relied on studies that had been conducted within the past 15–20 years. To avoid publication bias, published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008) using the terms lung neoplasm, carcinoma, small cell, chemotherapy and randomised controlled trial. The search was also guided by a thorough examination of reference lists from original articles, review articles, relevant books and the Physician Data Query registry of clinical trials.

selection of trials

Phase III randomised controlled trials were considered if they compared first-line, systemic chemotherapy for ED-SCLC that included cytotoxic agents, providing year of trial initiation. Trials were excluded if they investigated immunotherapeutic regimens or if they enrolled only responders to the initial round of chemotherapy. Trials that were initially designed to assess combined modality treatments, including radiotherapy and surgery concurrently with the initial chemotherapy, were also considered ineligible, whereas those involving the sequential use of these therapies or prophylactic cranial irradiation (PCI) after the induction of chemotherapy were allowed. Some phase III trials included patients with both LD- and ED-SCLC. These were considered eligible only if survival data for the patients with ED-SCLC could be obtained. The definitions of LD- and ED-SCLC varied somewhat in the different groups, but we could not reallocate the patients because of our inability to access each patient database. Instead, we applied the definitions described in each original report to this study. If no relevant descriptions were documented, we assumed that the definitions in the trial were based on the guidelines that existed at the time the trial was initiated [6, 7]. The control arms in each phase III trial were identified based on the statement in each trial.

data abstraction

To avoid bias in the data-abstraction process, four medical oncologists (IO, NO, YF and KH), one of whom holds a board certificate for medical oncology (KH), independently abstracted the data from the trials and subsequently compared the results. The following information was obtained from each report: the year of trial initiation (year when the first patient was accrued), the number of patients enrolled and randomised, the median patient age, the proportion of patients who had a good performance status (PS), the proportion of patients who were male and who had brain metastasis, the chemotherapeutic regimen, the definition of ED, the description of the administration of sequential thoracic irradiation, surgery or PCI as part of the trial design and the MST (per treatment arm). All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. For trials with more than two treatment arms, we constructed multiple pairs for the investigational and reference arms.

quantitative data synthesis

To investigate the association between differences in ORR and MST, we defined the MST difference as the difference in MST between the investigation and reference arms; similarly, the ORR difference was defined as the ratio of the ORR in the investigation arm to the ORR in the reference arm (all measures in months). The information from the phase III trials was evaluated using a multiple stepwise regression model (with the following stepping method criteria: probability of F to enter of ≤ 0.05 and to remove of ≥ 0.10) to determine whether the following factors independently affected the MST difference: ORR difference, year of study, definition of ED, ratio of patients with a good PS in the investigational arm to those in the reference arm and a trial design including PCI for those with an OR (CR/PR) to the induction of chemotherapy. All analyses were weighted by trial size. The data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies. All P values corresponded to two-sided tests; significance was set at $P < 0.05$. The strength of each association was defined a priori using commonly accepted criteria for the proportion of variation (R^2) as follows: 0–0.29, little or no association; 0.30–0.69, moderate or weak association and 0.70–1.00, strong association [8].

results

trials included in the analysis

Of the 2166 trials screened, 48 trials for ED-SCLC were identified as having data regarding OS and ORR (Figure 1). A total of 8779 patients were randomly allocated to 100 chemotherapeutic arms. Of these 48 trials, two had three treatment arms and one had four treatment arms; thus, 52 trial pairs were in the investigational arm versus the reference arm (Table 1). Of these trials, most had high proportions of male patients and patients with a good PS. The response criteria were described in 43 of the 52 trials. Approximately half of the trials used the response criteria of the World Health Organisation (WHO). Regarding the chemotherapeutic regimens, cisplatin plus etoposide-containing regimens were most frequently evaluated in both the investigational and reference arms (25 and 27 arms, respectively), while a cyclophosphamide, adriamycin and vincristine regimen was used in 17 and 23 arms, respectively.

degree of association between the MST and ORR differences

We plotted the MST and ORR differences (Figure 2). A modest relationship was detected between the ORR and MST differences ($R^2 = 0.3314$), suggesting that the ORR difference between the investigational and reference arms could predict 33.1% of the variance in the MST difference between the arms.

Next, we assumed that this association would be closer if the trials were limited to those in which the response criteria were clearly defined; the relationship between the two parameters, however, was not as so different as expected ($n = 43$; $R^2 = 0.1949$). In addition, we assessed whether the association could be affected by the type of response criteria, but it was nearly consistent irrespective of using the WHO criteria for response assessment [$R^2 = 0.1340$ ($n = 23$) versus 0.2765 ($n = 20$) for those trials in which the WHO criteria and other criteria were used, respectively].

To rule out potential confounding variables between the ORR difference and other trial characteristics, we conducted a multiple linear regression analysis for the MST difference. The stepwise multiple regression model used excluded all covariates

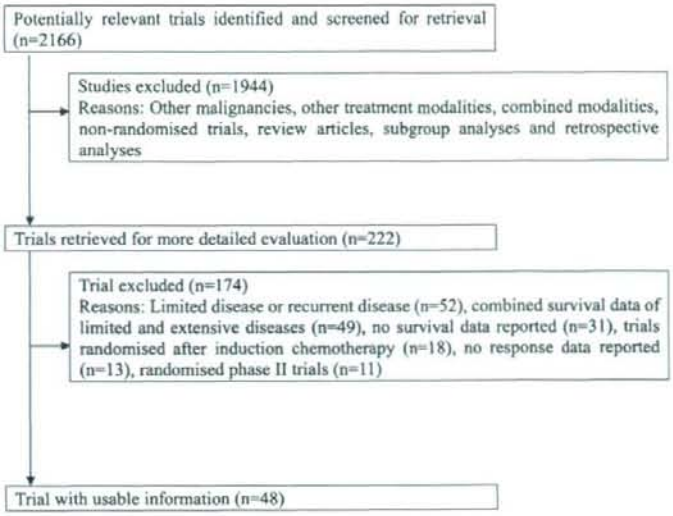

Figure 1. Flowchart showing the review process for the trials.

Table 1. Trial demographics and chemotherapeutic regimens in the 52 trial pairs

Trial characteristics	
Median no. of randomly assigned patients per trial (range)	142 (33–784)
Published year (median, range)	1997 (1990–2008)
Year of trial initiation (median, range)	1990 (1983–2006)
Percentage of patients with a good PS (median, range)	80 (35–100)
Percentage of male patients (median, range)	81 (56–93)
Trials including the administration of PCI to those with an objective response to the initial treatment (yes/no)	20/32
Definition of extensive disease (yes/no)	36/16
Description of the response criteria (yes/no)	43/9
World Health Organisation	23
European Cooperative Oncology Group	2
RECIST	1
Japan Lung Cancer Society	1
Described, but no criteria type documented	16

Good PS was defined as a PS of zero or one.
PS, performance status; PCI, prophylactic cranial irradiation; RECIST, response evaluation criteria in solid tumours.

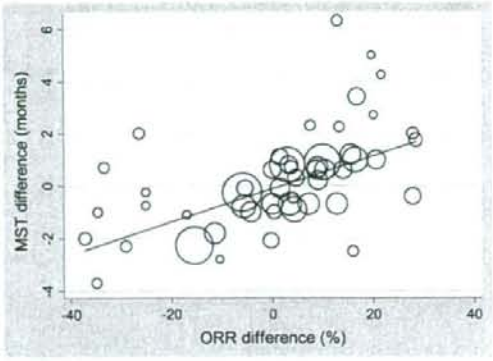

Figure 2. Correlations between the median survival time (MST) difference between the investigational and reference arms and differences in the objective response rate (ORR) in the eligible trial pairs weighted by the number of randomised patients ($R^2 = 0.3314$). The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain 33.1% of the variance in the MST difference between the arms. Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

except the ORR difference. This turned out to be a significant factor affecting the MST difference ($P = 0.003$); however, only 31.6% of the variance in the MST ratio was accounted for even by this model ($R^2 = 0.3156$).

association between the MST and ORR differences in several subgroups

To investigate whether the trial setting could affect the relationship between the MST and ORR differences, eligible

Table 2. Degree of association between the ORR and MST differences in various clinical settings in the simple regression analysis

	No. of trials	Regression coefficient	R^2
Overall	52	0.063	0.3314
Various subgroups			
Trials including PCI for those with an objective response to the initial therapy			
Yes	20	0.083	0.6279
No	32	0.053	0.2254
CAV regimen			
Yes	24	0.062	0.3302
No	28	0.063	0.3264
PE regimen			
Yes	32	0.062	0.3376
No	20	0.064	0.3185
Trial design of additional thoracic irradiation			
Yes	14	0.061	0.4954
No	38	0.063	0.2937
Published year			
1996 or before	26	0.037	0.2346
1997 or later	26	0.094	0.4671
% of good PS patients			
≥80[a]	12	0.061	0.3351
<80[a]	13	0.092	0.4505

All analyses were weighted by trial size.
[a]Median percent of patients with good PS.
ORR, objective response rate; MST, median survival time; R^2, the proportion of variation; PCI, prophylactic cranial irradiation; CAV, cyclophosphamide, doxorubicin and vincristine; PE, cisplatin and etoposide; PS, performance status.

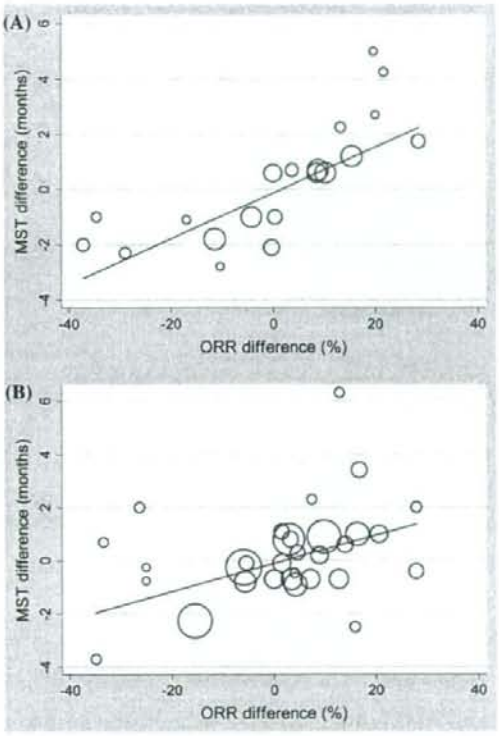

Figure 3. Correlations between the median survival time (MST) difference and objective response rate (ORR) difference between the investigational and reference arms in trials (**A**) designed to administer prophylactic cranial irradiation (PCI) to those with an objective response to the inductive therapy ($R^2 = 0.6279$) or (**B**) not ($R^2 = 0.2254$). The analysis was weighted by the number of randomised patients. The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain as much as 62.8% of the variance in the MST difference between the arms in trials including PCI, while in the trials without PCI, the MST difference was less exactly accounted for by the ORR difference (22.5%). Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

trial pairs were divided into several subgroups (Table 2). We found a stronger association between the two parameters for those trials in which all the patients with an OR to the initial chemotherapy were given PCI ($R^2 = 0.6279$; Figure 3A), whereas a weaker association was found in those trials without that type of design ($R^2 = 0.2254$; Figure 3B). None of the other characteristics assessed seemed to affect the association (Table 2).

predicted MST difference based on the fitted model for those trials with the PCI setting

We next constructed a fitted formula for predicting the MST difference using the actual ORR difference for those trials that included PCI as part of their design in which a high R^2 value was obtained:

> Predicted MST difference between the investigational and reference arms = 0.083 × (actual ORR difference) − 0.125.

The predicted MST differences are listed in Table 3 according to the various ORR differences. For example, when the investigational regimen was expected to yield a 10% increase in the ORR as compared with the state-of-the-art regimen, the MST was predicted to increase only by 0.7 months (21.2 days) in the investigational arm.

discussion

In this study, we found a modest association between the ORR and MST differences in the complete trial ($R^2 = 0.3314$; Figure 2). In contrast, the design of PCI setting for all responders to the initial chemotherapy favourably affected the relationship ($R^2 = 0.6279$; Figure 3A). In this setting, large differences in ORR were needed to predict a survival benefit (1.2-day survival advantage per 2% increase in ORR).

Note that the relationship was stronger only for those trials in which PCI was assigned to all patients with an OR to the initial treatment ($R^2 = 0.6279$; Figure 3A). One would postulate that this result is related to the ability of anticancer agents to penetrate the blood–brain barrier (BBB). Apart from clinically

Table 3. Predicted MST difference according to the ORR difference

ORR difference* (%)	Predicted MST difference*, months (days)
2.5	0.1 (2.5)
5.0	0.3 (8.7)
7.5	0.5 (14.9)
10.0	0.7 (21.2)
12.5	0.9 (27.4)
15.0	1.2 (33.6)
17.5	1.4 (39.8)
20.0	1.6 (46.1)

*Difference between the investigational and reference arms. For example, when an investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by 0.7 months (21.2 days) in the investigational arm.
ORR, objective response rate; MST, median survival time.

obvious cranial metastases, which would be sensitive to systemic chemotherapy because of an impaired BBB [9], radiologically undetected micrometastases in the brain, which are common in patients with ED-SCLC, are generally considered to be insensitive to chemotherapy because they are able to hide behind the still-intact BBB [9]. Thus, even if systemic chemotherapy was effective against detectable extracranial diseases, such small undetectable cranial diseases could continue to grow without the use of PCI, possibly resulting in a poor outcome. That could explain why a tight association was not observed between the radiological response and survival data. However, with the PCI setting for responders to the initial chemotherapy, such a difference in the response pattern between extracranial and intracranial diseases would theoretically be minimised. This may be why a stronger association between the radiological response and survival was observed when only those trials that included PCI as part of their design were assessed in the analysis (Figure 3A). This hypothesis requires further study. Other clinical factors including PS examined did not seem to influence the relationship between ORR and MST (Table 2), while a number of studies have shown that PS has impacts on outcome [10–12]. This would simply reflect that good PS patients can respond well to chemotherapies and survive longer and that poor PS patients hardly respond to them, resulting in the poor outcome.

In addition, knowing how much of a difference in ORR is needed to predict an obvious survival difference in ED-SCLC is also clinically necessary. In their abstracted database study, Johnson et al. [13] investigated the role of ORR as a surrogate marker in the treatment of advanced non-small-cell lung cancer (NSCLC) by comparing incremental differences in MST between the arms with those in ORR. The formula they used to predict the MST difference was nearly identical to ours, except for the difference in cancer type: MST difference = 0.090 × (the ORR difference) − 0.048. Using this formula for patients with NSCLC, if the investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by only 0.9 months (25.6 days) in the investigational arm. Given either formula, one could intuitively predict the survival benefit of a new therapy by comparing the OR data from their early clinical trials with the ORR for the state-of-the-art therapy. At any rate, both sets of results indicate that, irrespective of the small- or non-small-cell subtype, the survival advantage would be small even if a relatively large ORR difference was obtained.

Few randomised trials of metastatic lung cancer have reported hazard ratios, and predictions based on this measure would not be representative and could be biased. Additionally, differences in follow-up duration between trials could affect the calculated hazard ratios. For these reasons, the MST was used in this study to ensure that all trials were long enough to capture the relevant end points in at least half of the patients. The reason for this pragmatic approach is that the value of a treatment of metastatic disease is usually measured in terms of incremental survival gains rather than the proportional or absolute risk of death [13].

Trial-level surrogacy as described here is not necessarily linked to individual-level surrogacy; thus, our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. Analyses based on data derived from both sources have strengths and weaknesses [14]. Although the use of individual patient data (IPD) restricts the analysis to a limited number of trials and the analysis is not easily replicated by independent researchers, it allows better characterisation of important covariates that affect survival. Future investigations using IPD could show a more precise relationship between survival and the response to treatment. In addition, as a point to be discussed, assessment of response rate would be variable and unreliable. It is well documented that response rates have dropped in recent years as more rigorous criteria are used. This is borne out by the fact that the correlation dropped in studies with clearly defined response criteria. Using differences in response rates rather than absolute values would help address this.

In conclusion, in this study, we found a favourable relationship between the ORR and MST differences for trials in which those who responded to the initial chemotherapy subsequently received PCI. Given the recent finding of a survival advantage from PCI even in patients with ED-SCLC [15], the frequency at which PCI is used for responders to the initial treatment will likely increase. Considering such circumstances, ORR data may be useful for predicting how much improvement in OS can be obtained. In contrast, large differences in ORR are needed to predict a survival benefit, strongly suggesting the need for the development of new chemotherapeutic agents in ED-SCLC.

funding

There is no funding source in this study.

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Prognosis of Small Adenocarcinoma of the Lung Based on Thin-Section Computed Tomography and Pathological Preparations

Mizuki-Ikehara, MD, Haruhiro Saito, MD,† Kouzo Yamada, MD,† Fumihiro Oshita, MD,† Kazumasa Noda, MD,† Haruhiko Nakayama, MD,† Kazuo Masui, MD,‡ Yoichi Kameda, MD,‡ Yuko Komase, MD,* and Teruomi Miyazawa, MD,**

Objective: We investigated the relationship between findings from tumor opacity in the mediastinal window image and solid lesions in pathological preparations and related the results to tumor recurrence.
Methods: The subjects were 115 patients with a lung adenocarcinoma of 20 mm or smaller who underwent surgical resection. The proportion of the reduction in the tumor opacity in the mediastinal window image maximum diameter to the maximum diameter of the tumor opacity was calculated as the reduction percentage, and the proportion of the maximum solid lesions in pathological preparation diameter to the maximum tumor diameter was calculated as the pathological ratio.
Results: The incidence of relapse was significantly higher in patients with a reduction percentage of less than 50% and in patients with a pathological ratio of less than 50%.
Conclusions: Measurement of the reduction percentage and the pathological ratio may allow prediction of prognosis of small adenocarcinoma of the lung.

Key Words: small adenocarcinoma, lung, thin-section CT, solid lesion, prognosis

(*J Comput Assist Tomogr* 2008;32:426–431)

Early detection and early treatment of lung cancer is of importance to improve therapeutic outcomes. Introduction of computed tomography (CT) screening and advancement of diagnostic CT imaging have enabled early detection and early diagnosis of small peripheral-type lung cancers,[1] and such cases are mostly adenocarcinoma. The potential to diagnose and treat peripheral small adenocarcinoma is likely to increase, and qualitative diagnosis is important for establishment of therapeutic policies. Although a small diameter is one of the characteristics of early cancers, a subgroup of small peripheral-type lung cancers are already invasive despite early detection. Patz et al[2] reported that the tumor diameter is not correlated with disease extent or prognosis of small lung cancers of 30 mm or less in diameter, suggesting that other criteria are necessary for prediction of prognosis of peripheral-type early cancers. The current standard therapy for peripheral-type lung adenocarcinoma is lobectomy with lymph node dissection if applicable. However, a subgroup of cases with small adenocarcinoma of the lung have a good prognosis even with limited surgery, and if the prognostic factors in early cancer could be defined, the indication for limited surgery may expand.

A study performed at Kanagawa Cancer Center previously found that the tumor opacity in the mediastinal window image (TOM) of thin-section CT (TS-CT) is associated with the prognosis of patients with lung adenocarcinoma of 20 mm or smaller in diameter.[3,4] However, the pathology of the TOM has not been fully investigated; therefore, in this study, we examined whether TS-CT findings reflect pathological findings in detail and determined the association of tumor opacity with prognosis.

MATERIALS AND METHODS

This study was approved by the institutional Review Boards of Kanagawa Cancer Center and St. Marianna University School of Medicine. Informed consent was obtained from each patient before operation. The subjects were 115 patients with peripheral-type adenocarcinoma of the lung who underwent surgical resection at the Kanagawa Cancer Center between January 1997 and October 2003. Patients with bronchioloalveolar carcinoma (BAC) undetectable in the mediastinal window image were excluded. Contrast-enhanced CT scans were performed using an Aquilion M/16 or X-Vigor/Real system (Toshiba Medical Systems, Tokyo, Japan). High-resolution images targeted to the tumor were obtained at 120 kV (peak) and 200 mA using sections of 2-mm thickness. Images were photographed on each sheet of film using mediastinal (level, 40 Hounsfield unit [HU]; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings.

The findings of TS-CT was evaluated and measured the maximum diameter of the TOM in TS-CT. The proportion of the reduction in the maximum TOM diameter relative to the

From the *Division of Respiratory and Infectious Diseases, Department of Internal Medicine, St Marianna University School of Medicine; †Department of Thoracic Oncology and ‡Pathology, Kanagawa Cancer Center, Yokohama, Japan.
Received for publication March 26, 2007; accepted May 15, 2007.
Reprints: Mizuki Ikehara, MD, Division of Respiratory and Infectious Diseases, Department of Internal Medicine, St. Marianna University School of Medicine, Yasashi-cho 1197-1, Asahi-ku, Yokohama, 241-0811, Japan (e-mail: mizukiikehara@aol.com).
This study was supported in part by a grant from 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.

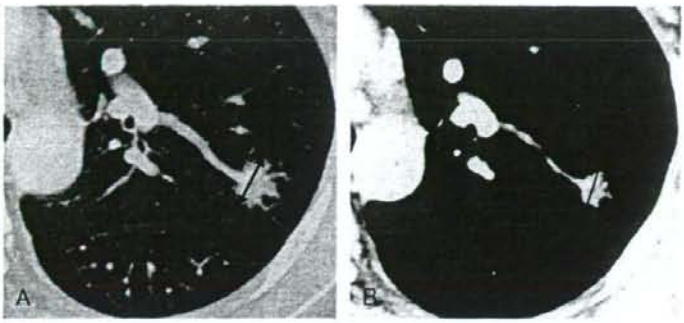

FIGURE 1. Adenocarcinoma with mixed subtypes. TS-CT lung window image (A) and TS-CT mediastinal window image (B). Reduction percentage (%) = {[Tumor diameter (lung window: black arrow) − Tumor diameter (mediastinal window: black line)]/ Tumor diameter (lung window)} ×100.

maximum diameter of the tumor opacity in the lung window was calculated as the reduction percentage (Fig. 1).

The excised lung was distended and fixed by infusion of formalin from the bronchus. The specimen including the maximum cross-sectional area of the tumor was sliced into several sections at intervals of a few millimeters and stained with hematoxylin and eosin. The maximum diameter of the solid lesion in the pathological preparation (SLP) observed under a magnifying glass was measured. The SLP was defined as follows: (1) regions with alveolar collapse, (2) regions accompanied by destruction of the alveolar framework, and (3) regions described in (2) accompanied by collagen fibrotic foci. The proportion of the maximum SLP diameter to the maximum tumor diameter in the pathological preparation was calculated as the pathological ratio (Fig. 2).

Comparisons between the maximum diameters of the tumor opacity in the lung window in TS-CT and the maximum diameters in the pathological preparation, between the maximum TOM and SLP diameters, and between the reduction percentage and pathological ratio were performed using Pearson correlation coefficient.

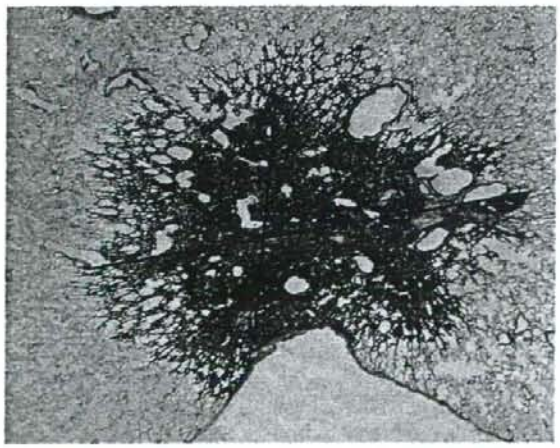

FIGURE 2. Adenocarcinoma with mixed subtypes. Pathological ratio (%) = {[Tumor diameter (black line) − Maximum diameter of solid lesion (black arrow)]/Tumor diameter} ×100.

To investigate the association with prognosis, the relationships of relapse with the maximum TOM and SLP diameters, reduction percentage, and pathological ratio were analyzed by the Kaplan-Meier method and subjected to log-rank tests.

RESULTS

The background characteristics of the patients are shown in Table 1. The patients comprised 52 men and 63 women and had a median age of 67 years. The disease stage was Ia in 95 patients, Ib in 10, IIa in 2, IIb in 3, IIIa in 4, and IIIb in 1, and cancer recurred in 16 patients (13.9%). Of the 115 patients, 99 patients underwent lobectomy with systemic hilar and mediastinal lymph node dissection, whereas 16 patients underwent wedge resection. There were no recurrences in patients who underwent wedge resection. None of the cases had been treated by radiotherapy or chemotherapy.

Pathological findings are shown in Table 2. All cases included alveolar collapse, destruction of the alveolar framework, or collagen fibrotic foci. The histological types were determined according to the World Health Organization classification: the tumor was of the acinar type in 1 case, papillary type in 8, BAC in 12, adenocarcinoma with mixed subtypes in 80, and solid adenocarcinoma with mucin in 14. The Noguchi classification[5] was type B (localized BAC [LBAC] with foci of structural collapse of alveoli) in 12 cases, type C (LBAC with foci of active fibroblastic proliferation) in 80, type D (poorly differentiated adenocarcinoma) in 14, type E (tubular adenocarcinoma) in one, and type F (papillary adenocarcinoma with a compressive growth pattern) in 8. Lymphatic invasion was noted in 21

TABLE 1. Patient Characteristics

Characteristic	No.
No. patients	115
Sex (male/female)	52/63
Age (median, range)	67 (29–82)
p-stage	
I (Ia/Ib)	95/10
II (IIa/IIb)	2/3
III (IIIa/IIIb)	4/1
Relapse	16

TABLE 2. Pathological Findings

	No. (%)
Subtypes of adenocarcinoma	
Acinar	1 (0.9)
Papillary	8 (7.0)
BAC	12 (10.4)
Adenocarcinoma with mixed subtypes	80 (69.6)
Solid adenocarcinoma with mucin	14 (12.1)
Noguchi classification	
Type B	12 (10.4)
Type C	80 (69.6)
Type D	14 (12.1)
Type E	1 (0.9)
Type F	8 (7.0)
Lymphatic permeation	21 (18.3)
Vascular invasion	33 (28.7)
Pleural involvement	17 (14.8)
Nodal involvement	9 (7.8)

Type A indicates LBAC; type B, LBAC with foci of structural collapse of alveoli; type C, LBAC with foci of active fibroblastic proliferation; type D, poorly differentiated adenocarcinoma; type E, tubular adenocarcinoma; type F, papillary adenocarcinoma with a compressive growth pattern.

cases (18.3%), vascular invasion in 33 (28.7%), pleural invasion in 17 (14.8%), and lymph node metastasis in 9 (7.8%).

Tumor diameter-related parameters are shown in Table 3. In TS-CT findings, the median tumor diameter was 18 mm, the median maximum TOM diameter was 12 mm, and the median reduction percentage was 25%. In the pathological preparation, the median tumor diameter was 14 mm, the median maximum SLP diameter was 10 mm, and the median pathological ratio was 24.1%. An analysis of the correlation between the TS-CT and pathological findings gave correlation coefficients of 0.714 ($P < 0.0001$) for the relationship between the maximum diameter of the tumor opacity in the lung window and the pathological maximum tumor diameter, 0.874 ($P < 0.0001$) for the relationship between the maximum TOM and SLP diameters, and 0.903 ($P < 0.0001$) for the relationship between the reduction percentage and pathological ratio.

Analysis of the association of relapse with the maximum TOM and SLP diameters, reduction percentage,

TABLE 3. Maximum Diameters in TS-CT and in Pathological Preparations and the Reduction Percentage and Pathological Ratio (n = 115)

	Size, mm
TS-CT	
Tumor diameter in lung window images, median (range)	18 (8–28)
Tumor diameter in mediastinal window images, median (range)	12 (1–22)
Reduction percentage, median (range)	25 (0–88.9)
Pathological preparation	
Pathological tumor diameter, median (range)	14 (4–20)
Maximum diameter of solid lesions, median (range)	10 (1–20)
Pathological ratio, median (range)	24.1 (0–84.5)

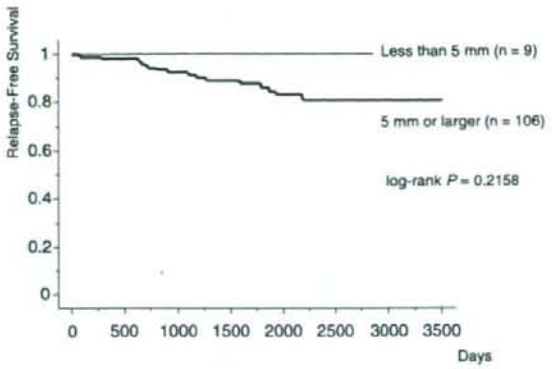

FIGURE 3. Maximum TOM diameter in TS-CT and relapse-free survival.

and pathological ratio gave the following results. Relapse did not occur in patients with a maximum TOM diameter of less than 5 mm, but the difference in incidence of relapse between these patients and those with a maximum TOM diameter of 5 mm or greater was not significant by log-rank test (Fig. 3). The maximum TOM diameter was less than 5 mm in 9 cases, accounting for 7.8% of all cases. Statistically, no significant difference was noted in the incidence of relapse examined at various cutoff values with maximum TOM diameter. However, the incidence of relapse was significantly higher in patients with a reduction percentage of less than 50% compared with those with a reduction percentage of 50% or greater (log-rank test, $P = 0.0203$); no relapse occurred in patients with a reduction percentage of 50% or greater (Fig. 4). No relapse was prominent for in the 28 cases with a reduction percentage of 50% or greater, which accounted for 24.3% of all cases. Regarding the pathological preparations, relapse occurred in only 1 patient with a maximum SLP diameter of less than 5 mm, but there was no significant difference in the incidence of relapse between patients with maximum SLP diameters of less than 5 mm and 5 mm or greater (Fig. 5). The maximum SLP diameter was less than 5 mm in 15 cases, accounting for 13.0% of all cases. Statistically, there was no

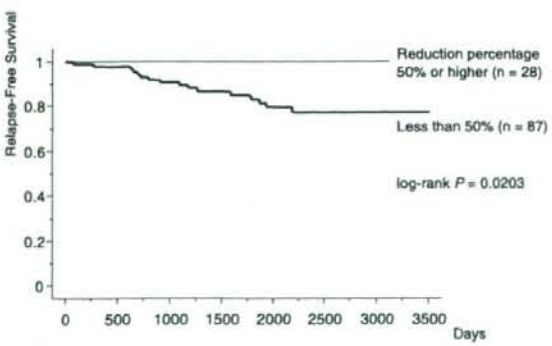

FIGURE 4. Reduction percentage in TS-CT and relapse-free survival.

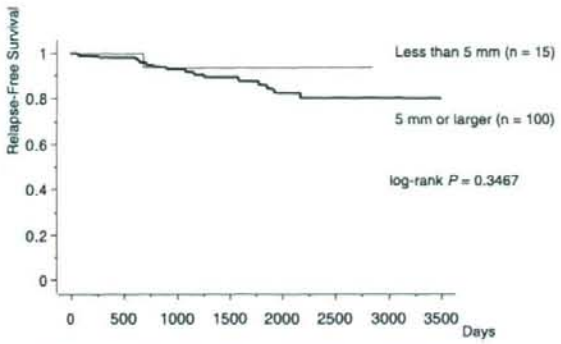

FIGURE 5. Maximum SLP diameter in pathological preparations and relapse-free survival.

significant difference in the incidence of relapse examined at various cutoff values with the maximum SLP diameter. However, the incidence of relapse was significantly higher in patients with a pathological ratio of less than 50% compared with those with a pathological ratio of 50% or greater (log-rank test, $P = 0.0493$); no relapse occurred in patients with a pathological ratio of 50% or greater (Fig. 6). No relapse occurred in the 20 cases with a pathological ratio of 50% or greater, which accounted for 17.4% of all cases.

No acinar, papillary, or solid adenocarcinoma with mucin subtype was noted pathologically when the reduction percentage and pathological ratio exceeded 50%, nor was there vascular, lymphatic, or pleural invasion or lymph node metastasis in such cases (Tables 4 and 5).

DISCUSSION

A previous report from Kanagawa Cancer Center showed that cases of lung adenocarcinoma of 20 mm or smaller in diameter can be divided into 2 groups with different prognoses, based on the reduction percentage of the area in the mediastinal window image in TS-CT compared with the area in the peripheral window image in TS-CT being 50% or greater (air-containing type) and less than 50% (solid-density type).[3,4] Relapse did not occur in patients with tumors

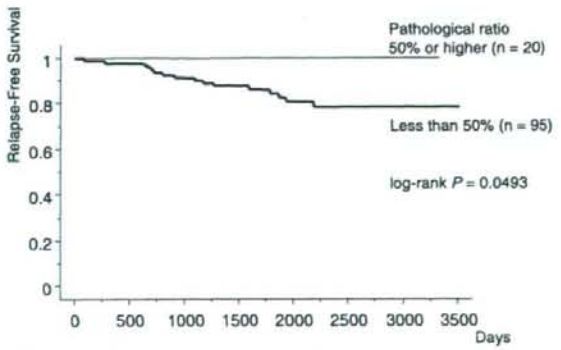

FIGURE 6. Pathological ratio in pathological preparations and relapse-free survival.

TABLE 4. Relationship Between a Reduction Percentage of Less Than 50% in TS-CT and the Pathological Findings

	Reduction Percentage ≥50% (n = 28)	Reduction Percentage <50% (n = 87)
Subtypes of adenocarcinoma		
Acinar	0	1
Papillary	0	8
BAC	8	4
Adenocarcinoma with mixed subtypes	20	60
Solid adenocarcinoma with mucin	0	14
Noguchi classification		
Type B	8	4
Type C	20	60
Type D	0	14
Type E	0	1
Type F	0	8
Lymphatic permeation	0	21
Vascular invasion	0	33
Pleural involvement	0	17
Nodal involvement	0	9

of the air-containing type, whereas recurrence was noted in approximately 25% of solid-density type cases, suggesting that a reduction percentage of 50% or greater is a positive prognostic factor. Tumors of the air-containing type belonged to BAC, whereas tumors of the solid-density type belonged to acinar, papillary, adenocarcinoma with mixed subtypes, or solid adenocarcinoma with mucin. Evaluation of the reduction percentage in the major axis of the tumor, which is a simpler approach, may also be a positive prognostic factor. In this study, we investigated the pathological validity of these

TABLE 5. Relationship Between a Pathological Ratio of Less Than 50% in the Pathological Preparation and Pathological Findings

	Pathological Ratio ≥50% (n = 20)	Pathological Ratio <50% (n = 95)
Subtypes of adenocarcinoma		
Acinar	0	1
Papillary	0	8
BAC	8	4
Adenocarcinoma with mixed subtypes	12	68
Solid adenocarcinoma with mucin	0	14
Noguchi classification		
Type B	8	4
Type C	12	68
Type D	0	14
Type E	0	1
Type F	0	8
Lymphatic permeation	0	21
Vascular invasion	0	33
Pleural involvement	0	17
Nodal involvement	0	9

imaging studies by comparing the maximum diameters of tumor opacity in the lung window (TOM) and the reduction percentage in TS-CT with the maximum diameters of the tumor (SLP) and the pathological ratio in the pathological preparation.

The air-containing category includes ground-glass opacity (GGO) tumors whose reduction percentage is 100%; GGO tumors have been identified as BAC with good prognosis.[6–10] Actually, relapse did not occur in all 53 cases with a reduction percentage of 100% that underwent surgical resection at Kanagawa Cancer Center between January 1997 and October 2003. Therefore, we excluded these cases. With exclusion of GGO tumors, differentiation of lesions into good and poor prognosis groups using TS-CT may be useful,[11] but the prognostic factors have not been fully investigated. Based on Pearson correlation coefficients, our data suggest a strong relationship between TS-CT findings and pathological findings for the relationships between the maximum TOM and SLP diameters and between the reduction percentage and pathological ratio. However, the relationship between the maximum tumor diameters in the TS-CT image and pathological preparation was slightly weaker. These findings suggest that the tumor opacity in the TS-CT mediastinal window faithfully reflects the SLP. The correlation coefficient between the reduction percentage and the pathological ratio was particularly high, showing that contrasting the mediastinal window image with the lung window image faithfully reflects the pathological findings. We note that slicing the excised lung in the same direction as that used for CT is difficult, and alteration of the size of air-containing lesions by formalin fixation is likely; however, the influence of these variables on the relationship between the reduction percentage and pathological ratio seems to be negligible.

Suzuki et al[12] and Yokose et al[13] have reported that the maximum diameter of the central scar may be associated with the prognosis of lung adenocarcinoma of 30 mm or lesser in diameter; these studies indicated that carcinoma did not recur, and qualitative diagnosis of cancer was possible in cases with a central scar diameter of 5 mm or smaller.

Definitions differ in SLP and the central scar. However, in our patients, recurrence did occur in some cases, although the maximum SLP diameter was 4 mm, suggesting that the maximum SLP diameter alone is insufficient for judgment of good prognosis (Fig. 7). The recurrent cases were solid adenocarcinoma with mucin, which did not show a lepidic growth pattern. Because the incidence of relapse is high in this type, the maximum SLP diameter may not serve as a prognostic factor.[5] In fact, there was no significant difference in the incidence of relapse between cases with a maximum SLP diameter of 5 mm or greater and less than 5 mm. In contrast, there was a significant difference in the incidence of relapse between cases with a pathological ratio of 50% or greater and less than 50%. These findings suggest that the pathological ratio may be more useful than the maximum SLP diameter for prediction of relapse.

In TS-CT, there was no significant difference in the incidence of relapse between cases with a maximum TOM diameter of 5 mm or greater and less than 5 mm. Although a significant difference was found in the incidence of relapse between cases with a reduction percentage of 50% or greater and less than 50%. Ohde et al[14] have reported that the prognosis was significantly better when the major axis of the tumor consolidation on the lung window image in TS-CT was 50% or less of the entire tumor diameter, and our results suggest that the reduction percentage is more useful than the maximum TOM diameter for prediction of relapse.

The pathological examination indicated that the solid lesions were the following: (1) regions with alveolar collapse, (2) regions accompanied by destruction of the alveolar framework, and (3) regions described in (2) that were accompanied by collagen fibrotic foci. Noguchi et al[5] classified the histopathology of small adenocarcinoma of the lung and found that destruction of the alveolar framework and collagen fibrotic foci were associated with prognosis; therefore, solid lesions in the pathological preparation may have contained a region associated with invasiveness of lung adenocarcinoma. Goto et al[15] reported that prognosis varied depending on the condition of the alveolar framework in lung adenocarcinoma of 20 mm or smaller in diameter and that prognosis was significantly poorer in cases with destruction of the alveolar framework associated with destruction of the basement membrane, suggesting that destruction of the basement membrane is the first step in tumor invasion. Because tumor invasion is accompanied by destruction of the alveolar framework and collagen fibrosis, the alveolar air space may be lost, resulting in formation of a solid region in the pathological preparation.

A lepidic growth and advancement pattern of the adenocarcinoma was noted in 80% of our cases, supporting the hypothesis that the early stage of lung adenocarcinoma is often BAC. In this growth and advancement pattern, the air-containing region is initially retained because the lesion

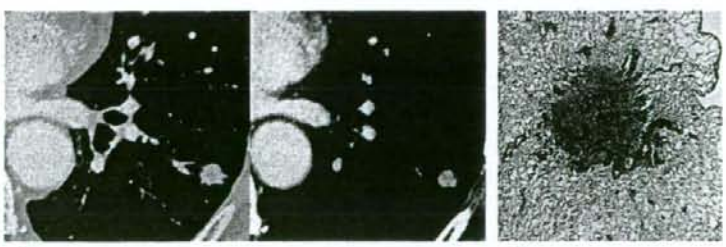

FIGURE 7. A recurrent case with a maximum SLP diameter of 4 mm. Solid adenocarcinoma with mucin: TS-CT (A); pathological preparation (B).

grows by replacement of alveolar lining cells, but acquisition of invasiveness is accompanied by destruction of the alveolar framework and collagen fibrosis, which decreases the air-containing region and increases the solid region. Therefore, decreases in the reduction percentage and pathological ratio may represent a state in which increased invasiveness has caused a decreased air-containing region and an increased solid region. Acinar, papillary, or solid adenocarcinoma with mucin are tumors with nonlepidic growth pattern, and prognosis of them is worse than tumors with lepidic growth pattern (BAC).[5] Pathological ratio and reduction percentage of tumors with nonlepidic growth pattern were less than 50% (Tables 4 and 5).

The correlation coefficient between the reduction percentage in TS-CT and the pathological ratio was very high, and no relapse occurred in cases with a reduction percentage exceeding 50%, confirming that the reduction percentage accurately reflects the pathological findings. Therefore, use of the reduction percentage in TS-CT to roughly divide lesions into 2 groups with different prognoses may be valid based on the pathological investigation. Measurements of the reduction percentage and pathological ratio may allow identification of lung adenocarcinoma with good prognosis. Such measurements are straightforward during intraoperative rapid diagnosis and may be useful for prediction of relapse and judgment of the indication for clinical treatment of early cancer. These findings suggest that prospective investigations of the indications for limited surgery and postoperative adjuvant therapy should be performed for small adenocarcinoma of the lung.

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