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Abbreviations:
A_z = area under alternative free-response ROC curve
CAD = computer-aided diagnosis
ROC = receiver operating characteristic

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Pulmonary Nodules at Chest CT: Effect of Computer-aided Diagnosis on Radiologists' Detection Performance[1]

PURPOSE: To evaluate the effect of computer-aided diagnosis (CAD) on radiologists' detection of pulmonary nodules.

MATERIALS AND METHODS: Fifty chest computed tomographic (CT) examination cases were used. The mean nodule size was 0.81 cm ± 0.60 (SD) (range, 0.3–2.9 cm). Alternative free-response receiver operating characteristic (ROC) analysis with a continuous rating scale was used to compare the observers' performance in detecting nodules with and without use of CAD. Five board-certified radiologists and five radiology residents participated in an observer performance study. First they were asked to rate the probability of nodule presence without using CAD; then they were asked to rate the probability of nodule presence by using CAD.

RESULTS: For all radiologists, the mean areas under the best-fit alternative free-response ROC curves (A_z) without and with CAD were 0.64 ± 0.08 and 0.67 ± 0.09, respectively, indicating a significant difference ($P < .01$). For the five board-certified radiologists, the mean A_z values without and with CAD were 0.63 ± 0.08 and 0.66 ± 0.09, respectively, indicating a significant difference ($P < .01$). For the five resident radiologists, the mean A_z values without and with CAD were 0.66 ± 0.04 and 0.68 ± 0.04, respectively, indicating a significant difference ($P = .02$). At observer performance analyses, there were no significant differences in A_z values obtained either without ($P = .61$) or with ($P = .88$) CAD between the board-certified radiologists and the residents. For all radiologists, in the detection of pulmonary nodules 1.0 cm in diameter or smaller, the mean A_z values without and with CAD were 0.60 ± 0.11 and 0.64 ± 0.11, respectively, indicating a significant difference ($P < .01$).

CONCLUSION: Use of the CAD system improved the board-certified radiologists' and residents' detection of pulmonary nodules at chest CT.

Helical computed tomography (CT) of the chest is the imaging modality with the highest sensitivity for the detection of pulmonary nodules. Lung cancer screening with low-radiation-dose helical CT has gained attention during the past 10 years (1–8). It has been reported that the detection rate of lung cancer screening with low-dose CT is 2.6- to tenfold higher than that with chest radiography (2–4,8). It has also been reported that stage I cancers represent 56%–93% of the lung cancers detected by using low-dose CT. These data suggest that this modality can help detect lung cancer at an earlier stage than chest radiography can (1–8). Therefore, low-dose CT is a promising method for lung cancer detection.

In the screening for lung cancer with CT, however, radiologists have to analyze large amounts of data, numerous image sections per case, and 50–100 cases per day. There is always the risk of missing a lesion. In a retrospective study of first annual CT examinations, Swensen et al (7) found that nodules were missed in 26% of patients. There are some methods to help avoid missing a pulmonary nodule, such as independent reading by two or more radiologists and the use of computer-aided diagnosis (CAD) for the detection of pulmonary nodules. Some researchers have reported the use of a CAD system in lung

cancer screening with CT (9–18). We also have developed an integrated CAD system for lung cancer screening with CT (19). The purpose of the present study was to evaluate the effect of using a CAD system on radiologists' performance in detecting pulmonary nodules.

MATERIALS AND METHODS

Case Selection

During the 12 months of 2001, 198 patients who were suspected of having pulmonary nodules at chest radiography were sent to Rinku General Medical Center for further examination with CT. Of the 198 patients, 133 gave consent for their CT data to be used for CAD research. This study was approved by the institutional review board of Rinku General Medical Center. The 133 cases were those of 65 men and 68 women aged 26–81 years (mean age, 57.4 years). The mean age of the men was 55.9 years (age range, 28–81 years), and the mean age of the women was 58.9 years (age range, 26–80 years).

All chest CT examinations were performed by using a LightSpeed QX/i scanner (GE Medical Systems, Milwaukee, Wis) without contrast material administration. Helical CT images of the entire lung were obtained by using a detector row width of 5.0 mm, helical pitch of 3.0, 7.5-mm section thickness and intervals, 0.8-second rotation time, 120 kVp, and 160–200 mA. Fifty-one of the 133 cases (of 133 patients) were excluded because of the presence of four or more pulmonary nodules, a pulmonary nodule larger than 3 cm in diameter, severe pulmonary fibrosis, diffuse bronchiectasis, or extensive inflammatory scars.

The chest CT images in the remaining 82 cases (of 82 patients) were reviewed for the location, number, and size of pulmonary nodules. The CT images obtained in the 133 cases were reviewed by two experienced radiologists (K.A. and S.H.) who did not participate in the observer performance study. K.A. and S.H. had more than 16 and 27 years of CT imaging experience, respectively. The two radiologists reviewed all images twice, with an interval of 1 month between the two review sessions. A final interpretation was performed by consensus.

The 82 cases were those of 29 patients without pulmonary nodules, 33 patients with one nodule, 15 patients with two nodules, and five patients with three nodules. The nodules examined in this study were located both centrally and peripherally in the lung parenchyma. In general, it is difficult to identify nodules smaller than 0.3 cm on 7.5-mm-thick CT image sections. Therefore, the two radiologists did not search for nodules smaller than 0.3 cm. As a result, the smallest nodules included in this study were 0.3 cm. The mean size of the 78 nodules was 0.89 cm ± 0.67 (SD) (range, 0.3–3.0 cm). Fifty-five nodules were 0.3–1.0 cm in diameter, and 23 nodules were 1.1–3.0 cm in diameter. A functional evaluation of our CAD system was performed by using these 82 cases.

Before the observer performance study, a pilot study was conducted with two observers, who were not involved in the observer performance study. It took these observers about 5 hours to read the images obtained in all 82 cases in the pilot study; this indicated that fatigue owing to reading would be an important factor in the observer performance study. For this reason, 50 of the 82 cases were randomly chosen for the observer performance study. These 50 cases were those of 14 patients without pulmonary nodules, 21 patients with one nodule, 10 patients with two nodules, and five patients with three nodules. The mean size of these 56 nodules was 0.81 cm ± 0.60 (range, 0.3–2.9 cm). Forty-five of these nodules were 0.3–1.0 cm in diameter, and 11 nodules were 1.1–2.9 cm in diameter. These 50 cases were those of 27 men and 23 women aged 28–81 years (mean age, 57.8 years). The mean age of the men was 56 years (age range, 28–81 years), and the mean age of the women was 60 years (age range, 42–73 years).

Computerized Scheme for Automated Detection of Pulmonary Nodules

Our method of nodule detection at CT is outlined in Figure 1. First, the lungs were segmented by using a gray-level threshold (−300 HU). The gray level selected for lung segmentation has resulted in the erroneous exclusion of nodules, vessels, and bronchi within the lungs. To compensate for this type of segmentation error, a three-dimensional labeling technique (20) and a mathematic morphologic technique (21) were used. Second, intrapulmonary structures such as pulmonary nodules, pulmonary vessels, and bronchi were segmented by using the top-hat transformation technique (22), with which a smoothed image is subtracted from the original image. Third, initial potential nodules were identified by using a sieve filter, which is used to analyze the intrapulmonary structures with the skeleton technique (22) and to select structures that are larger than a predefined size. The mesh size of the sieve filter is altered according to the section level in the vertical direction and the location within the lungs on individual sections.

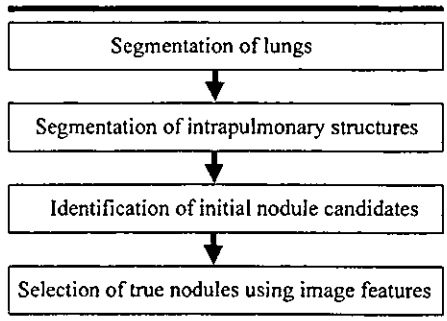

Figure 1. Diagram of the computerized scheme for detection of pulmonary nodules on CT images.

Finally, various image features of each potential nodule were assessed to separate true nodules from false-positive nodules. These image features included volume, roundness, average diameter, maximum diameter, diameter perpendicular to the maximum diameter, and distance between the potential nodule and the thoracic wall. An artificial neural network was applied to determine the likelihood of the lesion being a true nodule on the basis of the image features.

A workstation (Windows NT, PRIMERGY, with Dual Intel Pentium III [1.0-GHz] processors; Fujitsu, Tokyo, Japan) was used in this study, and the average nodule detection time for each case was about 7 minutes. To indicate the CAD output, the computer-detected location of each pulmonary nodule was marked by a small square, the center of which was placed in the center of the nodule. The computer-detected locations of potential nodules were marked by small squares. The true nodule was indicated by a large square. Figure 2 shows an example of this automatic nodule detection at chest CT.

Observer Performance Study

A total of 10 observers—five board-certified radiologists who did not specialize in chest radiology and five residents in radiology—took part in the observer performance study. The board-certified radiologists had 6–20 years of experience (mean, 11.4 years), and the residents had 2–4 years of experience (mean, 2.8 years). The sequential test method (23) was used

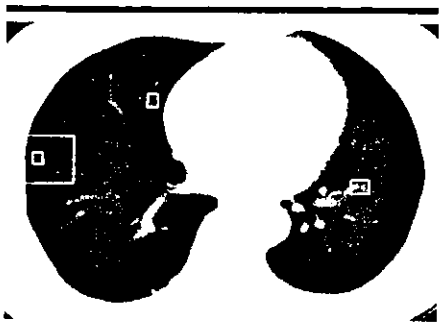

Figure 2. Automatic nodule detection on transverse chest CT image obtained at the level of the lower pulmonary veins. The computer-detected locations of the potential nodules are indicated by small squares. The true nodule is outlined by the large square.

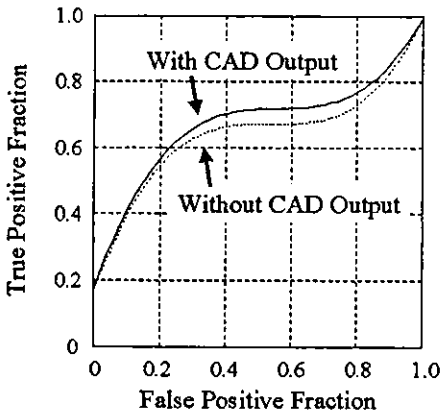

Figure 3. Averaged alternative free-response ROC curves for all observers in the detection of all pulmonary nodules without and with CAD output. The A_z values obtained without and with CAD output were 0.64 ± 0.08 and 0.67 ± 0.09, respectively, indicating a significant difference ($P < .01$).

in the observer performance study: Each observer first read the chest CT images independently and rated his or her confidence in determining the presence or absence of a nodule. The observer then performed the reading and rating again after seeing the results obtained by the CAD system. The observers were required to indicate only the presence or absence of a nodule without characterizing the lesions.

The results of automated detection of pulmonary nodules performed by using the NT workstation were stored in the database of a picture archiving and communication system, or PACS (HOPE/Dr ABLE-Ex; Fujitsu, Tokyo, Japan). The 10 observers read the CT images displayed on a gray-scale monitor (model SMM21200P; Siemens, Munich, Germany) with a spatial resolution of 2,048 × 2,560. The monitor screen could be split into up to 24 parts to display the CT images, and the observers were allowed to select the number of split parts on the monitor screen. They were also permitted to use the cine mode for displaying the images.

All 50 cases (of 50 patients) were presented to the observers in the same order. The observers were provided with the following information before the test to expedite the observer performance study: *(a)* The sequential test method was being used, *(b)* the cases of patients with nodules accounted for about 70% of all the cases, *(c)* the number of nodules was three or fewer in each case, and *(d)* the nodules were 0.3–3.0 cm in diameter. No restriction was placed on reading time.

Each observer used a continuous rating scale of a line-marking method to rate his or her confidence level by marking on a line that was 7 cm in length. The left end of the line indicated complete confidence that the chest CT image showed no nodule, whereas the right end indicated complete confidence that the chest CT image showed a nodule. Intermediate levels of confidence were indicated by the different positions of the marks between these two ends on the line, and positions close to the right and left ends indicated, respectively, greater and lesser degrees of confidence regarding the presence of a nodule. One author (H.H.) then measured the distance between the left end and the marked point and converted this distance to an ordinal confidence rating that ranged from 0 to 100.

The results of the initial review by the two radiologists (K.A., S.H.) who did not participate in the observer study were used as the reference standard. A continuous rating scale containing a pair of horizontal lines was used in the sequential test. Observers first recorded their non–computer-aided rating results on the upper line; then, they rerecorded their rating results on the lower line after seeing the CAD output. They entered the reading results for each case on a record form. This form had six sets of continuous rating scales containing two horizontal lines each (two sets each for up to three possible nodules). Each observer was required to mark the continuous rating scale to indicate his or her level of confidence regarding the presence or absence of a nodule in each case and to record the number of the section showing a nodule and the general schematic location of the nodule on the right side. Before the observer test, each observer underwent a training session that involved reading the images obtained in five training cases to become familiarized with the observer test. These five training cases were not a part of the 50 cases used in the observer performance study.

Statistical Analysis

Observer performance was evaluated by using alternative free-response receiver operating characteristic (ROC) analysis, in which one takes into account nodule location and which allows evaluation of multiple nodules per case (24,25). Alternative free-response ROC curves for each observer when not using and when using the CAD output were calculated by plotting the true-positive fraction against the likelihood of obtaining an image with false-positive findings (ie, with one or more false-positive lesions) at each confidence level. The area under each alternative free-response ROC curve (A_z) was used to compare the observers' performance in detecting pulmonary nodules when they did not use CAD with their performance when they did use CAD. Analyses of the detection of all nodules and of the detection of nodules 1 cm in diameter or smaller were performed.

The significance of the difference between the A_z values obtained without and those obtained with CAD outputs was evaluated with a two-tailed paired t test. The significance of the difference in A_z values between the board-certified radiologists and the radiology residents was evaluated with a two-tailed two-sample t test. P values of less than .05 were considered to indicate a significant difference. Statistical analyses were performed by using a statistical software package (StatView, version 5.0; SAS Institute, Cary, NC).

RESULTS

In the total of 82 cases (total of 78 pulmonary nodules), our CAD system identified 62 and missed 16 nodules, yielding a true-positive rate of 80%. The total number of sections scanned by our CAD system was 3,556, and the total number of nodules falsely detected was 3,092, yielding a false-positive rate of 0.87 nodule per section. The mean sizes of the 16 unidentified nodules and the 62 correctly identified nodules were 0.81 cm ± 0.60 (SD) (range, 0.3–2.4 cm) and 0.91 cm ± 0.70 (range, 0.3–3.0 cm), respectively. There was no significant difference in size between the unidentified and correctly identified nodules ($P = .58$).

The graph in Figure 3 shows the averaged alternative free-response ROC curves for all 10 observers in the detection of all pulmonary nodules. The A_z values for all

10 observers in the detection of all pulmonary nodules without and with CAD output are summarized in Table 1. The mean A_z values obtained without and with CAD output were 0.64 ± 0.08 and 0.67 ± 0.09, respectively, indicating a significant difference ($P < .01$).

Figure 4 shows the averaged alternative free-response ROC curves for the five board-certified radiologists in the detection of all pulmonary nodules. Figure 5 shows the averaged alternative free-response ROC curves for the five radiology residents in the detection of all pulmonary nodules. In the board-certified radiologist group, the mean A_z values obtained without and with CAD output were 0.63 ± 0.08 and 0.66 ± 0.09, respectively, indicating a significant difference ($P < .01$). In the resident group, the mean A_z values obtained without and with CAD output were 0.66 ± 0.04 and 0.68 ± 0.04, respectively, indicating a significant difference ($P = .02$). There was no significant difference in the mean A_z values obtained without ($P = .61$) and with ($P = .88$) CAD output between the two groups.

Figure 6 shows average alternative free-response ROC curves for all 10 observers in the detection of pulmonary nodules 1.0 cm in diameter or smaller. The A_z values for all 10 observers in the detection of pulmonary nodules 1.0 cm in diameter or smaller obtained without and with CAD output are summarized in Table 2. The A_z values were lower with than without CAD output for two of the 10 observers: one board-certified radiologist and one resident. The mean A_z values obtained without and with CAD output for all of the observers were 0.60 ± 0.11 and 0.64 ± 0.11, respectively, indicating a significant difference ($P < .01$).

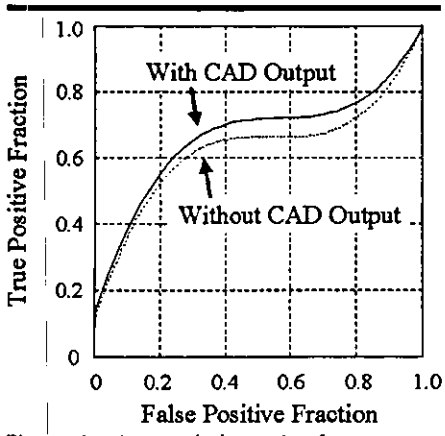

Figure 4. Averaged alternative free-response ROC curves for five board-certified radiologists in the detection of all pulmonary nodules without and with CAD output. The A_z values obtained without and with CAD output were 0.63 ± 0.08 and 0.66 ± 0.09, respectively, indicating a significant difference ($P < .01$).

TABLE 1
A_z Values for Performance in Detecting All Nodules

Observer No.	Without CAD Output	With CAD Output
Board-certified radiologists		
1	0.49	0.52
2	0.64	0.70
3	0.74	0.79
4	0.59	0.61
5	0.66	0.67
Radiology residents		
6	0.65	0.70
7	0.70	0.76
8	0.56	0.57
9	0.75	0.78
10	0.64	0.65

Note.—The mean A_z value for all observers (ie, board-certified radiologists and radiology residents) obtained without CAD was 0.64 ± 0.08 (SD), and the mean A_z value for all observers obtained with CAD was 0.67 ± 0.09.

DISCUSSION

There are a number of published studies on CAD systems that automatically detect pulmonary nodules on chest CT images (9–18). In the studies of Giger et al (9), Armato et al (12), and Lee et al (15), the researchers made clear reference to true-positive rates of 94%, 72%, and 72%, respectively, and false-positive rates of 0.08, 4.60, and 1.10 nodules per section, respectively, with the CAD system. On the other hand, our CAD system yielded a true-positive rate of 80% and a false-positive rate of 0.87 nodule per section. It is not known whether Giger et al (9), Armato et al (12), or Lee et al (15) used comparable exclusion criteria or similar instructions with regard to the number and prevalence of nodules to expect in each case. Therefore, it is difficult to compare our results with the results of these other studies.

A true-positive rate of 100%, a false-negative rate of 0%, and a false-positive rate of 0 nodule per section would be ideal. In fact, however, as the true-positive rate approaches 100%, the false-positive rate also tends to increase. Therefore, to develop a clinically useful automatic system for the detection of pulmonary nodules, an increased true-positive rate and decreased false-positive rate, with a sufficient balance between the two values, are necessary. With present technical levels, the developmental target of our CAD system is a true-positive rate of 90% or greater and a false-positive rate of 0.1 or fewer nodule per section. The reformation of our CAD system is ongoing.

The results of the observer study suggest that the use of our CAD system led to improved performance in the detection of pulmonary nodules at chest CT for both the radiology residents and the board-certified radiologists. There was no significant difference between the two groups in their performance in detecting pulmonary nodules either without or with CAD output. In the observer study, the observers were required only to detect pulmonary nodules: They were not required to determine the likelihood of malignancy of any lesions.

The basic knowledge required to detect pulmonary nodules is only the sectional anatomy of the lungs. All of the residents who took part in the observer study had 2 or more years of experience and were considered to be thoroughly familiar with the sectional anatomy of the lungs, like the board-certified radiologists. This factor presumably accounts for the finding that there was no significant difference between the two groups in their performance in detecting pulmonary nodules either without or with CAD output. In other words, radiologists' performance in detecting pulmonary nodules probably depends more on how attentively each observer reads CT images than on his or her experience and knowledge as a radiologist (with the exclusion of their knowledge of the sectional anatomy). In these conditions, the use of CAD is expected to improve radiologists' detection performance, irrespective of the knowledge or experience of each observer.

The A_z values for all the observers in the detection of nodules 1 cm in diameter or smaller were significantly higher with than without CAD output. However, for one board-certified radiologist and one radiology resident, the A_z values for the detection of these small nodules were lower with than without CAD output. In general, it is frequently difficult to distinguish a 1-cm or smaller nodule from the cross section of a blood vessel on an image with a relatively large (ie, 7.5–10.0-mm) section thickness. Reading on a workstation in cine mode is useful for tracing the continuity of a blood vessel (26). However, even in cine mode, it is frequently difficult to distinguish a small nodule of about 5 mm from a blood vessel on an image with a section thickness of 7.5–10.0 mm.

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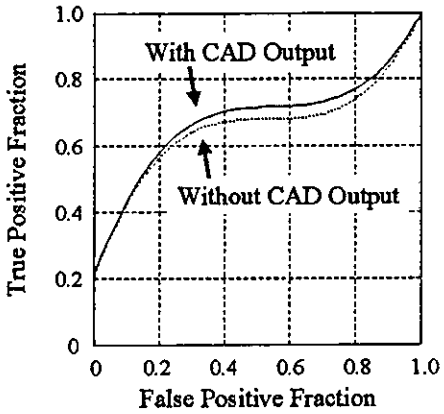

Figure 5. Averaged alternative free-response ROC curves for five radiology residents in the detection of all pulmonary nodules without and with CAD output. The A_z values obtained without and with CAD output were 0.66 ± 0.04 and 0.68 ± 0.04, respectively, indicating a significant difference (P = .02).

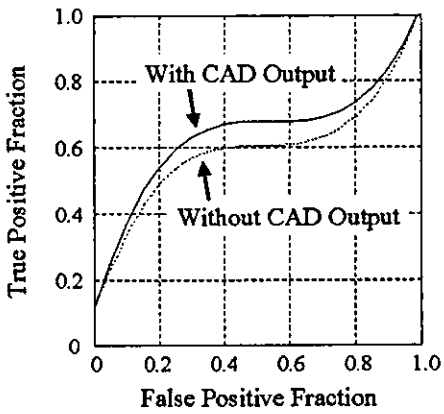

Figure 6. Averaged alternative free-response ROC curves for all observers in the detection of pulmonary nodules 1.0 cm in diameter or smaller without and with CAD output. The A_z values obtained without and with CAD output were 0.60 ± 0.11 and 0.64 ± 0.11, respectively, indicating a significant difference (P < .01).

TABLE 2
A_z Values for Performance in Detecting Nodules 1.0 cm or Smaller

Observer No.	Without CAD Output	With CAD Output
Board-certified radiologists		
1	0.47	0.54
2	0.61	0.68
3	0.73	0.72
4	0.64	0.71
5	0.72	0.79
Radiology residents		
6	0.74	0.77
7	0.41	0.44
8	0.60	0.58
9	0.48	0.53
10	0.55	0.69

Note.—The mean A_z value for all observers (ie, board-certified radiologists and radiology residents) obtained without CAD was 0.60 ± 0.11 (SD), and the mean A_z value for all observers obtained with CAD was 0.64 ± 0.11.

The present problem with our CAD system is a high false-positive rate. When a nodule is small—that is, 1 cm or smaller—it is difficult to verify in a short time the presence of such a small nodule that has been identified by using the CAD system. This appears to be the reason that the A_z values were lower with than without CAD output for two observers. Use of an image with a thin section thickness—that is, 1–2 mm—makes it easier to distinguish a nodule 1 cm or smaller from a blood vessel. However, our system was developed for use with relatively thick sections—that is, 5–10 mm. Therefore, it is necessary to develop a new system with which CAD can be used with images with section thicknesses of 1–2 mm.

The minimum target size of a nodule at CT lung cancer screening is important for setting scanning parameters (ie, section thickness, section interval, detector row width, helical pitch, and reconstruction algorithm) and determining the detection capacity of the CAD system. The minimum target size of a nodule must be decided with consideration of how much improvement in prognosis is sought, after confirming the correlation between the pulmonary nodule size and the prognosis. Although some study results suggest that pulmonary nodule size and prognosis do not necessarily correlate (27), the results of a study by Sobue et al (8) suggest that small lung cancers are associated with a better survival rate. According to the results of that study, the 5-year survival rate was almost 100% for patients with nodules 9 mm or smaller. However, they considered all nodules 9 mm or smaller in their analysis and did not include a breakdown of the 5-year survival rates for patients with pulmonary nodules 9 mm or smaller. Although we developed our CAD system with the aim of detecting nodules up to 3 mm in diameter out of convenience, more studies are needed to determine the actual minimum target size.

This study had several limitations. First, to expedite the observer performance study, we provided the observers with certain information, such as the number of nodules in each case, the sizes of the nodules, and the fact that the cases with nodules accounted for about 70% of the total number of cases. However, providing such information may have skewed the observational data. In daily clinical work, more nodules may actually be present. Furthermore, if the readers assume that only three nodules are present, they will stop searching for nodules after identifying three, even though they perceive that there are more, and, thus, the potentially false-positive reports will be artificially excluded.

Second, we excluded the cases of severe pulmonary fibrosis, diffuse bronchiectasis, and extensive inflammatory scars because lung segmentation with the CAD system may be difficult in cases with such severe interstitial lung disease. We also excluded the patients who had four or more pulmonary nodules and those who had pulmonary nodules larger than 3 cm in diameter. However, these exclusions may have biased the results in favor of the usefulness of the CAD system.

Third, we used the sequential test method in the observer performance study. However, reading the images without CAD output and then reading them with CAD output may have introduced a training effect.

Fourth, the observers were allowed to select the number of split parts on the monitor screen in the observer performance study; however, there might be a substantial difference in the conspicuity of nodules when the screen is one part or split into 24 parts to display CT images. This factor may partially explain the poorer performance of the radiologists as compared with that of the CAD system.

Fifth, we used the results of the initial review by the two experienced radiologists as a reference standard in the observer performance study; however, determining whether they accurately identified the "true" nodules is problematic. Pathologic confirmation for or clinical follow-up of patients to assess nodule growth patterns is necessary to identify and avoid missing the true nodules.

In conclusion, the use of our CAD system helped to improve both the residents' and the board-certified radiologists' performance in detecting pulmonary nodules. However, the next challenge is to decrease the false-positive rate associated with our CAD system.

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Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed small-cell lung cancer

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Irinotecan (CPT-11) has been shown to exhibit excellent antitumour activity against small-cell lung cancer (SCLC). A multi-institutional phase II study was therefore conducted to evaluate the efficacy and toxicity of CPT-11 combined with cisplatin (CDDP) and etoposide (ETOP) (PEI regimen) for the treatment of sensitive relapsed SCLC. Patients who responded to first-line chemotherapy but relapsed more than 8 weeks after the completion of first-line therapy ($n = 40$) were treated using the PEI regimen, which consisted of CDDP (25 mg m^{-2}) weekly for 9 weeks, ETOP (60 mg m^{-2}) for 3 days on weeks 1, 3, 5, 7, and 9, and CPT-11 (90 mg m^{-2}) on weeks 2, 4, 6, and 8 with granulocyte colony-stimulating factor support. Five complete responses and 26 partial responses were observed, and the overall response rate was 78% (95% confidence interval 61.5–89.2%). The median survival time was 11.8 months, and the estimated 1-year survival rate was 49%. Grade 3/4 leucocytopenia, neutropenia, and thrombocytopenia were observed in 55, 73, and 33% of the patients, respectively. Nonhaematological toxicities were mild and transient in all patients. In conclusion, the PEI regimen is considered to be highly active and well tolerated for the treatment of sensitive relapsed SCLC.
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Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumours, and first-line combination chemotherapy improves survival. However, despite a high response rate to chemotherapy, the majority of SCLC patients relapse. At the time of recurrence, the tumour is broadly resistant to second-line chemotherapy and is lethal within a few to several months (Glisson, 2003). The further development of not only first-line chemotherapy but also of effective salvage chemotherapies is needed.

In predicting the efficacy of salvage chemotherapy, two major factors are important: the response to the initial chemotherapy and the duration of time between the last exposure to chemotherapy and the confirmation of recurrence (Postmus *et al*, 1987; Giaccone *et al*, 1988; Ardizzoni *et al*, 1997; Ebi *et al*, 1997). Based on these factors, relapsed SCLC is now commonly classified into two main groups. Patients who both respond to the initial chemotherapy and relapse more than 2 or 3 months after the completion of chemotherapy are considered to be 'sensitive relapse' patients, while patients whose tumour is stable or progresses during the initial chemotherapy or who have a recurrence within 2 or 3 months after the completion of chemotherapy are considered to be 'refractory relapse' patients (Giaccone *et al*, 1988). Since the outcomes of salvage chemotherapy for relapsed SCLC patients are different between these two groups, the ratios of sensitive and refractory cases must be carefully considered when evaluating the results of clinical trials for second-line chemotherapy.

The combination of cisplatin (CDDP) and etoposide (ETOP) (PE regimen) has been the standard chemotherapeutic regimen for SCLC (Fukuoka *et al*, 1991; Ihde, 1992; Roth *et al*, 1992; Aisner, 1996). Moreover, PE is a reasonable second-line chemotherapy for relapsed SCLC after combination chemotherapy consisting of cyclophosphamide, doxorubicin (ADM), and vincristine (VCR) (CAV regimen); the likelihood of a response to this regimen is 40–50% (Evans *et al*, 1984; Porter *et al*, 1985). Since PE has a relatively mild toxicity profile, other cytotoxic agent can be combined with PE.

Irinotecan (CPT-11), a camptothecin derivative topoisomerase I inhibitor, has been shown to exhibit excellent antitumour activity against SCLC in monotherapy and in combination with CDDP (Masuda *et al*, 1992; Kudoh *et al*, 1998). Based on these results, the Japan Clinical Oncology Group (JCOG) conducted a randomised phase III trial comparing CPT-11 and CDDP (IP regimen) with standard PE for previously untreated extensive stage (ED) SCLC (JCOG 9511) (Noda *et al*, 2002). The response rates were significantly higher for IP than for PE, and overall survival was also significantly better for IP than for PE. This was the first study to show the superiority of any one regimen over PE for the

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treatment of ED SCLC, and IP has become one of the standard regimens for ED SCLC in Japan. Thereafter, several clinical trials of CPT-11-containing regimens for patients with limited disease (LD), ED, and relapsed SCLC have been conducted by Japanese clinical study groups (Masuda *et al*, 1998; Mori *et al*, 2002; Sekine *et al*, 2002).

Consequently, a phase I trial of CPT-11 combined with weekly CDDP (25 mg m $^{-2}$) and biweekly ETOP (60 mg m^{-2}) (PEI regimen) was conducted, and the recommended dose of 90 mg m^{-2} of CPT-11 was repeated every 2 weeks (JCOG 9507) (Sekine *et al*, 2003). This regimen showed promising antitumour activity in patients with untreated ED SCLC (response rate, 91%, 1-year survival rate 46%). Moreover, since the drug dose and treatment schedule can be easily modified in a weekly regimen, this protocol is considered to be suitable for relapsed SCLC patients, who usually present with severe haematological toxicities during salvage chemotherapy because of poor bone marrow reserve (Masuda *et al*, 1990; Faylona *et al*, 1995).

Based on these results, we conducted two phase II trials to evaluate the efficacy and toxicities of PEI in patients with sensitive and refractory relapsed SCLC, separately. In this paper, the final results for the sensitive relapsed SCLC group are reported.

PATIENTS AND METHODS

Patient selection

Patients with histologically or cytologically confirmed SCLC who respond to first-line chemotherapy or chemoradiotherapy and relapsed more than 8 weeks after the completion of first-line treatment were candidates for the present study. Additional eligibility criteria were as follows: (1) age of 75 years or younger; (2) performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (3) measurable disease; (4) adequate organ function as documented by a $4.0 \times 10^9 l^{-1} \leqslant$ WBC count $\leqslant 12.0 \times 10^9 l^{-1}$, haemoglobin level of $\geqslant 9.0\,g\,dl^{-1}$, platelet count of $\geqslant 100 \times 10^9 l^{-1}$, total serum bilirubin level of $\leqslant 1.5\,mg\,dl^{-1}$, a hepatic transaminase level of $\leqslant 2$ times the institutional upper limit of normal, a serum creatinine level of $\leqslant 1.5\,mg\,dl^{-1}$; and (5) written informed consent. Patients were not eligible for the study if they had experienced any of the following events: (1) massive pleural effusion requiring drainage; (2) prior radiotherapy with an irradiated area larger than one-third of the bone marrow volume; (3) active infection; (4) contraindications for the use of CPT-11, including diarrhoea, ileus, interstitial pulmonary fibrosis, massive ascites, or hypersensitive reaction to CPT-11; (5) serious concomitant medical illness, including severe heart disease, uncontrollable diabetes mellitus or hypertension; or (7) pregnancy or lactation. This study was approved by the institutional review board at each participating institution.

Treatment schedule

Figure 1 shows the treatment schema of the PEI regimen. CDDP (25 mg m^{-2}) was administered intravenously (i.v.) over 60 min on day 1 and at 1-week intervals for 9 weeks; ETOP (60 mg m^{-2}) was administered i.v. over 60 min on days 1–3 of weeks 1, 3, 5, 7, and 9; and CPT-11 (90 mg m^{-2}) was administered i.v. over 90 min on day 1 on weeks 2, 4, 6, and 8. Hydration (2000 ml) and granisetron (40 μg kg^{-1}) were given on day 1. After day 1 on week 2, granulocyte colony-stimulating factor (G-CSF) (50 μg m^{-2}) was administered routinely according to JCOG 9507 on days when the cytotoxic drugs were not given, unless the WBC count exceeded $10.0 \times 10^9 l^{-1}$. Patients were expected to complete at least six cycles of this regimen; if the toxicities were acceptable and the tumour responded to the treatment, a maximum of nine cycles of chemotherapy were performed.

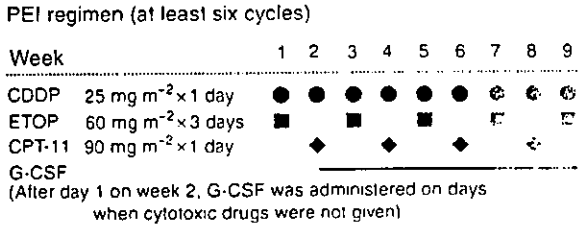

Figure 1 Treatment schedule

Toxicity assessment and treatment

During the course of treatment, complete blood cell counts and differential counts were analysed twice a week, and routine chemistry measurements and a chest X-ray were performed once a week. Toxicity was graded according to the toxicity criteria of the JCOG (Tobinai *et al*, 1993), a modified version of the NCI Common Toxicity Criteria issued in 1991. Grade 4 neutropenia was defined as $<0.5 \times 10^9 l^{-1}$, and grade 3 neutropenia was defined as between (and including) $0.5-1.0 \times 10^9 l^{-1}$, according to the JCOG criteria. The second and subsequent cycles of chemotherapy were delayed for 1 week if one of the following toxicities was noted on day 1: a WBC count of $<2.0 \times 10^9 l^{-1}$, a platelet count of $<50 \times 10^9 l^{-1}$, a serum creatinine level of $\geqslant 2.0\,mg\,dl^{-1}$, an elevated hepatic transaminase level or total serum bilirubin of grade 2 or higher, diarrhoea of grades 1–2, fever $\geqslant 38°C$, or a performance status of 3. The treatment was terminated if the above-mentioned criteria did not disappear in 3 weeks or if one of the following severe nonhaematological toxicities was noted: diarrhoea of grade 2 lasting for more than 1 week, diarrhoea of grade 3, neurotoxicity of grade 3, or drug-induced pneumonitis.

Dose modifications for toxicity

The CPT-11 dosage was reduced to 67.5 mg m^{-2} (25% reduction) in subsequent cycles if one of the following toxicities was noted: a WBC count of $<1.0 \times 10^9 l^{-1}$, or a platelet count of $<25 \times 10^9 l^{-1}$. If the above-mentioned toxicities reappeared after a 25% reduction in the dosage, the CPT-11 dosage was further reduced to 50 mg m^{-2} (44% reduction). Since CDDP (25 mg m^{-2}) and ETOP (60 mg m^{-2}) in this regimen were relatively low dose, no dose modifications for these drugs were permitted.

Pretreatment evaluation

Pretreatment assessment included a complete blood cell count, differential counts, routine chemistry measurements, creatinine clearance, blood gas analysis, electrocardiogram, chest X-rays, computed tomography (CT) scan of the chest, brain CT scan or magnetic resonance imaging (MRI), abdominal CT scan or ultrasound sonography, radionuclide bone scan, and bone X-rays, if indicated.

Response evaluation

Objective tumour responses were evaluated in all enrolled patients according to the WHO criteria issued in 1979 (WHO, 1979). A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) referred to a decrease in the total tumour size of at least 50% for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response and the appearance of no progressive or new lesions for at least 4 weeks. Progressive disease (PD) was

defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions. Patients whose responses were not evaluated were included in the analysis as not evaluable (NE).

Statistical methods

The primary end point of this study was the response rate, defined as the proportion of patients whose best response was CR or PR among all eligible patients, and its confidence interval was based on an exact binomial distribution. Simon's two-stage minimax design was used to determine the sample size and decision criteria. Assuming that a response rate of 40% in eligible patients would indicate a potential usefulness of the regimen while a rate of 20% would be the lower limit of interest and that alpha = 0.05 and beta = 0.20, the estimated number of required patients was 33 (Simon, 1989). Finally, this regimen would be considered worthy of further testing if 11 (33%) or more eligible patients showed an objective response. At the first stage decision, this regimen would be rejected if four (22%) or fewer of 18 eligible patients had an objective response. Thus, we determined that the sample size would be 35 registered patients. The planned accrual period was 2 years, and the follow-up period was set as 1 year after the completion of accrual. Secondary end points were toxicity and overall survival. The duration of overall survival was measured from the date of registration to the date of death from any cause or the last follow-up examination. Progression-free survival was calculated from the date of registration until evidence of PD. All patients started the treatment within 1 week of registration. The survival distribution was estimated by the method of Kaplan and Meier (1958).

RESULTS

Patient characteristics

From October 1998 to March 2001, 40 patients were enrolled in this study. The first-stage decision was made in October 1999, when 22 patients were registered. Three CRs and 13 PRs were observed in 18 analysed patients, resulting in a response rate of 89% (95% confidence interval (CI), 65.3–98.6%). This result did not meet the criteria for stopping the study as defined in the protocol, and the study was continued. At the time of the final analysis, there were three censored cases (8%). The median follow-up period for these cases was 25.5 months (range, 4.4–46.1 months).

The clinical characteristics of the enrolled patients are listed in Table 1. Of the 40 patients in the total, 29 (73%) were male and 11 (27%) were female; the median age was 67 years. A total of 39 patients (97%) had a good performance status of 0 or 1. The extent of the disease at the time of recurrence was LD in five patients (12%) and ED in 35 (88%). All 40 patients had been previously treated using platinum-based chemotherapy, such as PE in 11 patients, carboplatin plus ETOP in 11, PE plus weekly CDDP/VCR/ADM/ETOP (CODE) in six, CDDP plus CPT-11 in six, PEI in two, and other regimens in four. Eight (20%) of these patients received thoracic radiotherapy. All patients were eligible, and the toxicity and efficacy of the regimen was evaluated in all 40 patients.

Compliance with treatment

A total of 251 treatment cycles were administered, with a median of six cycles per patient (range, 1–9 cycles). A total of 32 patients (80%) completed six or more cycles of chemotherapy, and the median number of weeks for completing six cycles of chemotherapy was 7 weeks (range 6–10 weeks). Eight patients could not complete the planned six or more cycles for the following reasons: toxicities in four cases (grades 4 and 3 diarrhoea, grade 3 liver dysfunction, and grade 3 erythema); patient refusal in three cases; and PD in one case. Six patients (15%) had their dosage of CPT-11 reduced because of leucocytopenia in three, thrombocytopenia in two, and both in one.

Clinical response and survival

All the patients were included in the analyses of tumour response and survival. Five CRs (13%) and 26 PRs (65%) were observed, for an overall response rate of 78% (31 out of 40 patients; 95% CI, 61.5–89.2%). Four NC, four PD, and one NE were also observed. One patient was lost to follow-up and only two patients were still alive as of April 16, 2003. The median survival time (MST) was 11.8 months (95% CI, 10.1–13.5 months), and the estimated 1-year survival rate was 49% (Figure 2).

Table 1 Patient characteristics

Total no. of patients	40
Age, median (range)	67 (41–74)
Sex	
Male	29
Female	11
ECOG performance status	
0	9
1	30
2	1
Disease extent at relapse	
Limited disease	5
Extensive disease	35
Prior chemotherapy	
CDDP/ETOP	11
CBDCA/ETOP	11
CDDP/ETOP/CODE	6
CDDP/CPT-11	6
PEI	2
Others	4
Prior thoracic radiotherapy	8

ECOG = Eastern Cooperative Oncology Group; CDDP = cisplatin; ETOP = etoposide; CBDCA = carboplatin; CODE = cisplatin/vincristine/doxorubicin/etoposide; CPT-11 = irinotecan; PEI = cisplatin/etoposide/irinotecan.

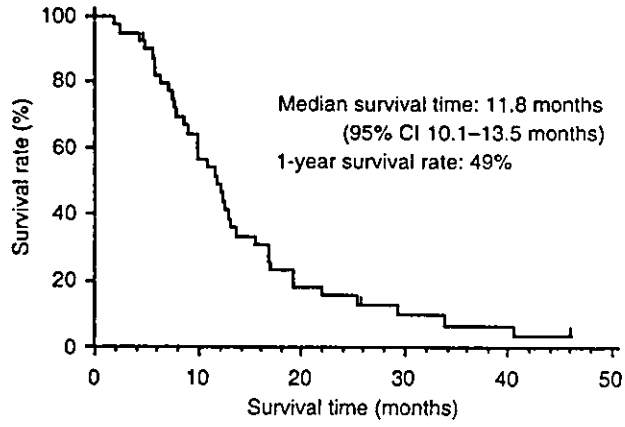

Figure 2 Overall survival ($n = 40$).

Site of first relapse and progression-free survival

The majority of patients ($n = 30$, 75%) experienced a systemic relapse after completing PEI, including 17 patients (43%) with central nerve metastases. Six patients (15%) developed only a locoregional recurrence, and one had no recurrence and died of acute myocardial infarction. No data on recurrence patterns were available in three patients because these patients were followed up at other hospitals. In all, 13 patients received additional chemotherapy treatment after recurrence (no data on response to third-line chemotherapy were available), while four patients underwent palliative chest radiotherapy and 18 underwent whole-brain irradiation for cerebral metastases. One patient, who achieved a CR by this regimen, developed a locoregional recurrence and underwent a right upper lobectomy. He has not experienced any further relapse and is still alive. The median progression-free survival period was 5.0 months (95% CI, 4.1–5.9 months) (Figure 3).

Toxicities

All the patients were included in the toxicity analysis. Severe toxicities were mainly haematological. Grades 3–4 leucopenia, neutropenia, and thrombocytopenia were observed in 22 (55%), 29 (73%), and 13 (33%) patients, respectively (Table 2). Nonhaematological toxicities were mild and transient in all patients. Grades 3–4 diarrhoea was noted in only three patients (8%) (Table 3). No treatment-related deaths occurred.

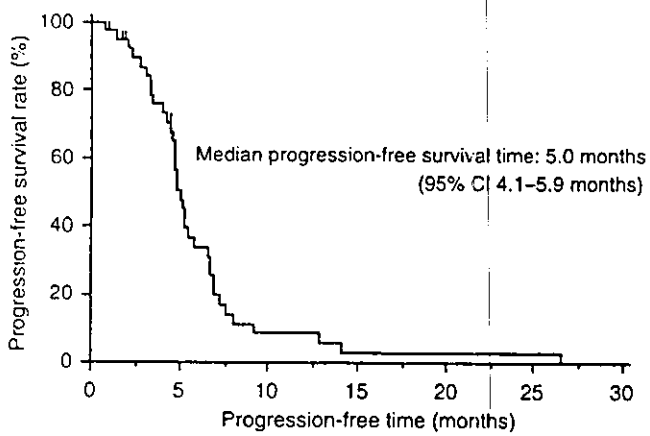

Figure 3 Progression-free survival ($n = 40$).

Table 2 Haematological toxicities (JCOG toxicity criteria)

	0	1	2	3	4	% of Grs 3 and 4
Leucocytopenia	2	3	13	17	5	55
Neutropenia	3	4	4	12	17	73
Anemia	2	4	16	18	—	45
Thrombocytopenia	10	7	10	7	6	33
Elevated total bilirubin	33	—	6	1	0	3
Elevated GOT	32	7	0	1	0	3
Elevated GPT	30	7	2	1	0	3
Elevated creatinine	37	3	0	0	0	0
Hyponatremia	28	4	6	0	2	5
Hypokalemia	32	5	3	0	0	0

Grs = grades; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 3 Nonhaematological toxicities (JCOG toxicity criteria)

	0	1	2	3	4	% of Grs 3 and 4
PS	1	30	4	5	0	13
Infection	28	4	7	1	0	3
Fever	29	7	4	0	0	0
Nausea/vomiting	11	15	11	3		8
Diarrhoea	15	16	6	2	1	8
Mucositis	36	4	0	0	0	0
Arrythmia	36	2	0	1	1	5
Eruption	37	1	1	1	0	3
Alopecia	16	17	7			
Allergy	39	0	1	0	0	0

Grs = grades; PS = performance status.

DISCUSSION

Despite a high response rate to first-line chemotherapy, most patients with SCLC experience a relapse within a year of the completion of therapy (Hansen, 1992). Although many relapsed patients in good physical condition undergo second-line chemotherapy, the results are disappointing. The obtained response is usually brief, and the median survival period is generally less than 4 months (Albain *et al*, 1993; Glisson, 2003).

Although one phase III trial for patients with relapse SCLC comparing the use of topotecan with CAV has been reported (von Pawel *et al*, 1999), a standard treatment for relapsed SCLC has not been agreed upon. However, the repeated use of the original induction regimen is the most popular treatment for sensitive relapsed patients. Reinduction chemotherapy has been reported to produce a response rate of 50%, and patients who relapsed more than 3 months after the end of their previous chemotherapy regimen were sensitive to reinduction chemotherapy (Giaccone *et al*, 1987; Postmus *et al*, 1987). Giaccone *et al* (1988) suggested that sensitive tumour cells, which were not completely eradicated by the induction chemotherapy, regrow spontaneously after the suspension of chemotherapy, eventually constituting a clinically significant part of the tumour burden. In the present study, two patients received the PEI regimen as a reinduction chemotherapy, and both patients showed PRs.

Many clinical trials of salvage chemotherapy for relapsed SCLC have been reported. In these studies, the single administration of CPT-11 or ETOP produced good results, with response rates of 16–47% and an MST of 3.5–6.2 months (Einhorn *et al*, 1990; Johnson *et al*, 1990; Masuda *et al*, 1992; Le Chevalier *et al*, 1997). Moreover, CPT-11 or ETOP-containing combined chemotherapy regimens showed favourable results, with response rates of 20–88% and an MST of 4.7–8.7 months (Table 4) (Evans *et al*, 1985; Masuda *et al*, 1990; Sculier *et al*, 1990; Gridelli *et al*, 1991; Roth *et al*, 1992; Faylona *et al*, 1995; Kubota *et al*, 1997; Masuda *et al*, 1998; Groen *et al*, 1999; Nakanishi *et al*, 1999; von Pawel *et al*, 1999; Domine *et al*, 2001; Kosmas *et al*, 2001). Therefore, these two drugs are considered to be key drugs for the treatment of relapsed SCLC. In particular, the combination of CPT-11 and ETOP (a combination of topoisomerase I and II inhibitors) produced a high response rate (71%) and the best survival results (MST, 8.7 months) (Masuda *et al*, 1998). In addition, a weekly chemotherapy regimen containing ETOP (CODE) was highly active in patients with relapsed SCLC, with a favourable response rate (88%) and survival duration (MST, 8.2 months) (Kubota *et al*, 1997). In the two studies mentioned above, four patients (16%) with refractory relapsed SCLC were included in the CPT-11 and ETOP study, and six patients (35%) with refractory relapsed SCLC were included in the CODE study. Three and five of these patients achieved PR, respectively.

ıle 4 Combination chemotherapy studies for relapsed small-cell lung

hor	Regimen	No. of pts	% of ref pts (%)	RR (%)	RR in ref pts (%)	MST (month)
er	CAV	61	75	21	5	6.2–7.5
Pawel	CAV	104	20	18	5	6.2
	CAV	41	32	12	8	NM
	PE	59	46	22	15	NM
s	PE	78	50	55	28	NM
ida	PE	20	NM	50	NM	4.7
elli	CCNU/MTX	33	100	21	21	4.0
na	PE/IFO	46	41	55	50	6.8
ita	CODE	17	35	88	83	8.2
ida	CPT-11/ETOP	25	16	71	75	8.7
inish	CPT-11/CDDP	5	100	20	20	NM
ine	GEM/PTX	31	58	50	40	NM
n	CBDCA/PTX	35	100	74	74	7.2
as	CDDP/IFO/PTX	33	61	73	70	6.5

patients, ref = refractory, RR = response rate, MST = median survival time; = cyclophosphamide/doxorubicin/vincristine, PE = cisplatin/etoposide, CCNU = stine, MTX = methotrexate, IFO = ifosfamide, CODE = cisplatin/vincristine/ ubicin/etoposide, CPT-11 = irinotecan, ETOP = etoposide; CDDP = cisplatin; = gemcitabine, PTX = paclitaxel, CBDCA = carboplatin; NM = not mentioned.

ıe response and survival data from Japanese clinical trials relapsed SCLC were generally better than those obtained vestern countries. We have no proof that this difference nds on either drug metabolism or tumour sensitivity. It ossibly related to the difference in patient follow-up interval een Japan and western countries. Since intensive follow after completion of first-line treatment is common in n, relapses can be detected in the early stage by CT or before becoming symptomatic. Therefore, relapsed patients a relatively good performance status, and showed good onses to second-line chemotherapy as well as better survival lts.

ıe weekly regimen was designed to increase the overall relative intensity of the chemotherapeutic drugs (Murray *et al*, 1991). ever, several phase III trials have made it clear that intensive dly chemotherapy does not improve the survival of patients SCLC (Furuse *et al*, 1998; Murray *et al*, 1999). On the other l, drug dosages and treatment schedules are easy to modify in dly chemotherapy regimens. Since patients with relapsed SCLC have lower bone marrow reserve, a high-dose regimen or nsified dosage can lead to treatment-related death (Masuda , 1990; Faylona *et al*, 1995). In the PEI regimen, the individual ge of each drug is within the commonly used range and the given at one time is lower than that of a standard 3-week cycle nen. The PEI regimen therefore permits greater flexibility in ge adjustment and treatment delays based on laboratory data he physical condition of patients. Thus, this regimen is idered to be suitable for the treatment of patients with relapse . In addition, this weekly schedule may be of great advantage nabling the synergistic effects of ETOP (a topoisomerase II bitor) and CPT-11 to be realised because the development of resistance to topoisomerase II inhibitors has been reported to increase tumour sensitivity to subsequent treatment with topoisomerase I inhibitors (Vasey and Kaye, 1997).

Three cytotoxic drugs were used in this PEI regimen. However, three-drug combination chemotherapy was reportedly associated with more severe toxicity and showed no survival benefit as compared with the two-dug combination (Mavroudis *et al*, 2001; Niell *et al*, 2002). The main reason for mild toxicities was that the PEI regimen consists of a weekly schedule. With a weekly chemotherapy regimen, drug dosages and treatment schedules can easily be adjusted according to haematological data and the patient's physical condition. These careful modifications resulted in a mild toxicity profile with the PEI regimen. Moreover, the PEI regimen did not consist of concomitant administration of three drugs but rather weekly alternative administration of a two-drug combination chemotherapy, that is, PE and IP. As a result, the toxicity profile was similar with that of two-drug combination chemotherapy.

Although all the patients in this study were sensitive relapsed cases, the overall response rate of 78% is one of the best results reported for relapsed SCLC. Moreover, although only selected patients with a good performance status were included in this study, it is notable that the median survival time was 11.8 months and the 1-year survival rate was 49%. In JCOG- 9511, the MST was 12.8 months in the IP arm and 9.4 months in the PE arm for chemotherapy naive ED SCLC patients (Noda *et al*, 2002). Our survival data for PEI is almost equivalent to that of first-line treatment. Salvage chemotherapy may be possible to prolong the survival of sensitive relapsed SCLC patients who are in good physical condition.

Since second-line chemotherapy for relapsed SCLC patients is a palliative treatment, a reasonable toxicity profile is essential. The main toxicities of the PEI regimen were haematological. Although G-CSF was routinely administered, Grades 3–4 leucopenia and neutropenia were observed in 55 and 73% of patients, respectively. Grades 3–4 thrombocytopenia was observed in 33% of patients. However, the frequencies of these haematological toxicities were approximately equal to that of first-line PE treatment (Noda *et al*, 2002). Nonhaematological toxicities were mild and transient in all patients. Grades 3–4 diarrhoea was noted in only three patients (8%). Irinotecan dose modifications as a result of haematological toxicities were only performed in six patients (15%). All toxicities were easily manageable, and no treatment-related deaths occurred.

In conclusion, PEI is a highly active and well-tolerated treatment for sensitive relapsed SCLC. Another phase II trial restricted to refractory relapsed SCLC patients is presently being performed by our clinical group. Further phase III studies comparing PEI regimen with rechallenges of the same drugs used in the first-line chemotherapy regimen should clarify the role of second-line chemotherapy for sensitive relapsed SCLC and are now being planned.

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S-1 Plus Cisplatin Combination Chemotherapy in Patients with Advanced Non–Small Cell Lung Cancer: A Multi-Institutional Phase II Trial

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ABSTRACT

Purpose: **To evaluate the efficacy and toxicity of a novel combination chemotherapeutic regimen including cisplatin with an oral anticancer agent, S-1 that consisted of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, for non–small-cell lung cancer (NSCLC) patients.**

Experimental Design: **In this phase II trial, patients with locally advanced and metastatic NSCLC were treated with the oral administration of S-1 at 40 mg/m^2 twice a day for 21 consecutive days while cisplatin (60 mg/m^2) was administered intravenously on day 8. This schedule was repeated every 5 weeks.**

Results: **Of 56 patients enrolled in the study, 55 patients were eligible and analyzed. The median number of cycles administered was 3 (range, 1–12 cycles). Among these 55 patients, one complete response and 25 partial responses were observed with an overall response rate of 47% (95% confidence interval, 34–61%). The median survival time was 11 months and the 1-year survival rate was 45%. Hematologic toxicities of grades 3 and 4 included neutropenia (29%) and anemia (22%). No grade 4 nonhematologic toxicity was observed. Grade 3 toxicity included anorexia (13%), vomiting (7%), or diarrhea (7%).**

Conclusions: **S-1 plus cisplatin combination chemotherapy showed a promising effectiveness with acceptable toxicity rates in patients with advanced NSCLC. These results warrant further investigations of this regimen including a randomized controlled trial for its use as a first line treatment for NSCLC.**

INTRODUCTION

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral anticancer agent comprised of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, in a molar ratio of 1:0.4:1 (1). Tegafur is a prodrug that generates 5-fruorouracil (5-FU) in the blood primarily via metabolism by liver enzyme cytochrome P450. 5-Chloro-2, 4-dihydroxypyridine enhances the serum 5-FU concentration by the competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. The inhibitory effect of 5-chloro-2, 4-dihydroxypyridine on dihydropyrimidine dehydrogenase *in vitro* is reported to be 180 times higher than that of uracil (2). Potassium oxonate is a reversible competitive inhibitor of orotate phosphoribosyl transferase, a phosphoenzyme for 5-FU. Diarrhea induced by 5-FU administration is thought to be attributable to the phosphorylation of 5-FU by the enzyme in the gastrointestinal tissue. After the oral administration of potassium oxonate, the concentration of potassium oxonate in the gastrointestinal tissue is high enough to inhibit the enzyme, and the concentration in blood and tumor is reported to be either slight or nil (3). Because of these mechanisms, oral S-1 administration generates a higher concentration of 5-FU than protracted intravenous injection of 5-FU given in a dose equimolar to the tegafur in S-1 whereas the incidence of adverse events concerning the gastrointestinal tract does not increase (4, 5).

In a phase II trial of S-1, which was orally administered at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced non–small-cell lung cancer (NSCLC) patients without prior chemotherapy, the response rate was 22% [95% confidence interval (CI), 12–35%] and the median survival time was 10.2 months. As expected, the incidence of severe gastrointestinal adverse events was low: *i.e.*, the incidence of grade 3 was 10% in anorexia, 8% in diarrhea, and 2% in stomatitis whereas no grade 4 nonhematologic adverse events were observed. In addition, there were few severe hematologic adverse events. The incidence of grade 3 or 4 was 7% in neutropenia, 2% in anemia, and 2% in thrombocytopenia (6).

UFT is another dihydropyrimidine dehydrogenase-inhibitory fluoropyrimidine consisting of tegafur and uracil in a 1:4 molar concentration (7). UFT has a similar profile of adverse events but a weaker antitumor activity against NSCLC than S-1 (8). However, combination chemotherapy consisting of a daily

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Note: additional participating institutions and principal investigators included National Shikoku Cancer Center Hospital (Yoshihiko Segawa), Jizankai Tsuboi Hospital (Koichi Hasegawa), Niigata Cancer Center Hospital (Akira Yokoyama), and Nippon Medical School (Akinobu Yoshimura).
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administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin at mid-cycle of administration of UFT for advanced non–small-cell lung cancer yields a response rate of 29 to 38% and a median survival time of 10 to 13 months (9–11).

With these backgrounds, we conducted a phase II trial combining the oral administration of S-1 for 21 days and a bolus injection of cisplatin on day 8 in patients with advanced NSCLC.

PATIENTS AND METHODS

Patient Eligibility. The patients were eligible for this phase II trial if they had been either cytologically or histologically confirmed to have NSCLC; stage IIIB without any indications for radiotherapy or stage IV; measurable disease; no prior treatment; an age range from 20 to 74 years; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and a projected life expectancy of at least 3 months. Other eligibility criteria for an organ function were as follows: a leukocyte count of 4,000 to 12,000/μL; platelet count ≥100,000/μL; hemoglobin level of ≥9 g/dl; a serum bilirubin level <1.5 mg/dl; serum aspartate aminotransferase and alanine aminotransferase levels <100 IU/L; alkaline phosphatase level of twice the upper limit or less; normal creatinine level; creatinine clearance rate of at least 60 mL/minute; partial pressure of arterial oxygen >70 Torr. For staging, all patients underwent a computed tomography scan of the thorax, including upper abdomen, and either a brain computed tomography scan or magnetic resonance images of brain, and a radioisotopic bone scan was also done in almost all patients.

Any patients who were pregnant or had concomitant serious diseases, a concomitant malignancy, pleural effusion necessitating treatment, or symptomatic cerebral involvement were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each of the participating institutions. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Tokyo Cooperative Oncology Group (Tokyo).

Treatment Schedule. S-1 capsule in the form of a 20 and 25 mg capsule containing 20 and 25 mg tegafur, respectively, was provided by the Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). S-1 was administered orally, 40 mg/m^2 twice a day, after meals between days 1 and 21. The actual dose of S-1 was selected as follows: in a patient with body surface area (BSA) < 1.25 m^2, 40 mg twice a day; BSA of 1.25 m^2 but <1.5 m^2, 50 mg twice a day; and BSA ≥ 1.5 m^2, 60 mg twice a day. Cisplatin (60 mg/m^2) was administered intravenously on day 8 when patients were hydrated with at least a 2,500 mL infusion. An antiemetic agent could be administered at the discretion of each patient's physician. The treatment regimen was repeated every 5 weeks at least two cycles unless disease progression or unacceptable toxicity occurred. A leukocyte count of ≥3,000/μL and the entry eligibility criteria regarding organ functions had to be satisfied to start the next cycle. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, the next cycle could be administered. The doses of S-1 were adjusted according to the degree of hematologic and nonhematologic toxicity. The dose was reduced by one level (20 mg per day) in patients whose BSA was ≥1.25 mg, with evidence of grade 4 hematologic toxicity or grade 3 or more nonhematologic toxicity during any cycle of administration. If recovery from such toxicities was confirmed at a reduced dose, administration at the reduced dose was continued. If a patient with BSA <1.25 m^2 experienced the above toxicities, then no further treatment with S-1 was done. If a rest period of >4 weeks was required, then the patient was withdrawn from the study.

Evaluation of Response and Toxicity. All eligible patients who received any part of the treatment were considered assessable for response and toxicity. Chest X-ray, complete blood count, and blood chemistry studies were repeated weekly. The response was assessed based on the chest X-ray or computed tomography scan findings that initially had been used to define the tumor extent. The response was evaluated in accordance with the criteria of the World Health Organization (12). A central radiological review was done to determine the eligibility of patients and the response of treatment. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical Analysis. The number of patients to be enrolled in this study was calculated to be 54, which was required to reject the null hypothesis that the lower bound of 95% CI of the expected response rate (50%) would be <30% under the conditions of α error of 0.025 (one side) and β error of 0.2. The overall survival of the eligible patients was defined as the time from the start of the treatment until death from any cause, and it was estimated by the Kaplan-Meier method. Differences between the proportions were evaluated by the χ^2 test. The data were considered to be significant when the P value was ≤0.05.

RESULTS

Patient Population. Between September 2000 and November 2001, 56 patients were enrolled in this study. One patient was considered to be ineligible because of prior treatment for pleurodesis in which OK432 was used for his malignant pleural effusion. The clinical characteristics of all eligible 55 patients are listed in Table 1. They included 41 men and 14 women, with a median age of 64 years. Thirty (55%) patients

Table 1 Patient characteristics

No. of patients	55
Age (years), median (range)	64 (46–74)
Gender	
Male	41 (75%)
Female	14 (26%)
Performance status (ECOG)	
0	30 (55%)
1	23 (42%)
2	2 (4%)
Stage	
IIIB	10 (18%)
IV	45 (82%)
Histology	
Adenocarcinoma	37 (67%)
Squamous cell carcinoma	14 (26%)
Others	4 (7%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.