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.

had Eastern Cooperative Oncology Group performance status of 0 and 45 (82%) patients had stage IV disease. The predominant histology type was adenocarcinoma (67%).

Response and Survival. Among all 55 eligible patients, 1 had a complete response and 25 had a partial response. Thus, the overall response rate was 47% (95% CI, 34–61%). Because one ineligible patient had a partial response, the overall response of all registered 56 patients was 48% (95% CI, 35–62%). The responding patients were classified in terms of the items shown in Table 2. There was no statistically significant difference in the response rates between the items compared. The median response duration was 4.2 months.

The median follow-up period was 28 months (range, 20–33 months). As shown in Fig. 1, median survival time of the 55 eligible patients was 11 months and the 1-year and 2-year survival rates were 45% (95% CI, 32–59%) and 17% (95% CI, 6–27%), respectively.

Adverse Events. The adverse events observed throughout the treatment of the 55 eligible patients are shown in Table 3. Among the hematologic adverse event, grade 3/4 neutropenia and anemia was observed in 29 and 22% of the patients, respectively. However, grade 3 thrombocytopenia was observed in only one patient (2%), and no patient had grade 4 thrombocytopenia. Among the observed nonhematologic adverse events, no grade 4 level was observed. There were no unexpected toxicities.

Table 2 Patient characteristics in relation to the response

Characteristics	No. of patients	Response				Response rate (%)
		CR	PR	NC	PD	
All	55	1	25	23	6	47
Gender						
Male	41	1	20	15	5	51
Female	14	0	5	8	1	36
Stage						
IIIB	10	0	4	5	1	40
IV	45	1	21	18	5	49
Histology						
Adenocarcinoma	37	0	15	17	5	41
Squamous cell carcinoma	14	1	7	5	1	57
Others	4	0	3	1	0	75

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

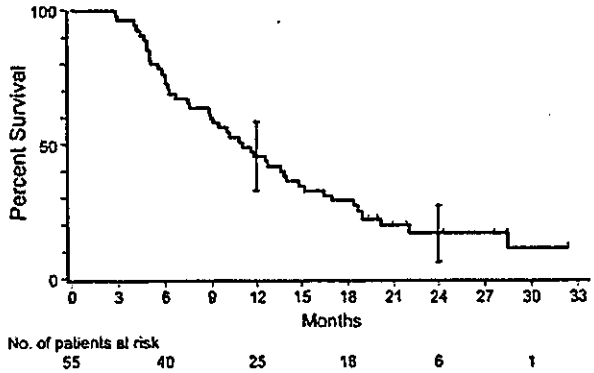

Fig. 1 Overall survival. Each *tick* represents a patient who is alive. The *bars* represent the 95% confidence interval of the survival rate at 1 year and 2 years after treatment.

Table 3 Hematologic and nonhematologic toxicities

Toxicity	Grade				Frequency of 3 or 4 (%)
	1	2	3	4	
Leukopenia	8	18	2	1	6
Neutropenia	7	13	13	3	29
Anemia	14	24	10	2	22
Thrombocytopenia	28	4	1	0	2
Aspartate aminotransferase	7	0	1	0	2
Alanine aminotransferase	6	1	1	0	2
Creatinine	9	1	1	0	2
Anorexia	21	15	7	0	13
Vomiting	14	3	4	0	7
Diarrhea	12	3	4	0	7
Stomatitis	12	2	0	0	0
Dermatitis	13	0	0	0	0

Compliance. A range of 1 to 12 treatment cycles were administered (1 cycle, 6 patients; 2 cycles, 18 patients; 3 cycles, 5 patients; 4 cycles, 12 patients; >4 cycles, 14 patients). The reasons for only one cycle of treatment were progressive disease in 4 patients and adverse events in 2 patients. The dose of S-1 was reduced in 8 patients because of adverse events including myelosuppression in 4 patients, gastrointestinal toxicity in 2 patients, glycemia in 1 patient, and dermatitis in 1 patient. A total of 197 cycles were given to the 55 patients. Sixty-nine (49%) of 142 treatment cycles excluding the first cycle was given at 4-week interval, 58 (40%) were at a 5-week interval, and 15 (11%) were at a >5-week interval.

DISCUSSION

Because the half-life of 5-FU is as short as 5 to 20 minutes (13) and the antitumor activity of 5-FU is time dependent, the continuous intravenous administration of 5-FU is considered to be appropriate rather than a bolus intravenous injection of 5-FU. In fact, a meta-analysis of six randomized trials in patients with colorectal cancer showed that the response rate was clearly higher for continuous infusion of 5-FU over 5 consecutive days than for weekly bolus injection of 5-FU (14). Although NSCLC has also been reported not to respond to a bolus injection of 5-FU (15), whether or not continuous treatment with 5-FU is effective for NSCLC remains unclear. However, studies have shown that a combination of cisplatin and protracted intravenous injection of 5-FU is effective for NSCLC (16). In prior trials, we used this combination chemotherapy with daily oral administration of UFT in place of the protracted intravenous injection of 5-FU which negatively affects the quality of life of a patient for advanced NSCLC (9–11).

The combination chemotherapy of cisplatin and 5-FU has been proven to have synergic antitumor effect in many experimental and clinical studies (17, 18). However, the optimal sequence for the administration of these drugs has yet to be determined. The sequence of cisplatin followed by 5-FU has been shown to be more cytotoxic than the reverse succession in *in vitro* and *in vivo* studies (19, 20) whereas the sequence of 5-FU followed by cisplatin has been proven to have a greater

antitumor activity than the opposite order of administration in tumor-bearing animals (21). Therefore, in our prior trials using UFT, we designed a treatment regimen that is thought to be a compromise solution between the present conflicting experimental data; namely, a daily administration of UFT from day 1 to 14 or 21 and a bolus infusion of cisplatin on day 8 (9, 10).

In the present study with S-1, the treatment modality was determined based on the UFT trials (9, 10) and phase I/II trial of S-1 combined with cisplatin in patients with advanced gastric cancer (22). The dose of cisplatin was decreased from 80 mg/m^2 in prior UFT trial to 60 mg/m^2 in the present trial because phase I trial indicated that 60 mg/m^2 of cisplatin on day 8 was the recommended dose when it was combined with daily administration of S-1 from day 1 for 3 weeks (22). Concerning the dose of cisplatin in combination chemotherapy in NSCLC patients, the effect of the dosage on survival has not yet been clearly elucidated. Klastersky *et al.* (23) reported the median survival time of patients who received vindesine plus combination chemotherapy consisting of either 60 or 120 mg/m^2 of cisplatin to be 7.6 and 6.4 months, respectively, and no overall survival difference between the two groups was observed ($P = 0.138$). On the other hand, the incidence of adverse events was significantly higher in the 120-mg dose than that in 60-mg dose.

Although a comparison between the present S-1 trial and the prior UFT trial with 108 patients (10) has limitation because of different trials, the response rate and survival seems to be favorable in the present trial despite the fact that proportion of stage IV patients in the present trial was higher than that in the UFT trials (82% *versus* 68%). The response rate and median survival time was 47% and 11.2 months in the present study and 29% and 10 months in the UFT trial, respectively. The frequency of severe adverse events in the both trials was similarly low.

The standard chemotherapy regimen for NSCLC is considered to be a platinum-based two-drug combination chemotherapy that uses paclitaxel, docetaxel, gemcitabine, or vinorelbine. The response rate and median survival time in the recent phase III trials that use these combination chemotherapies have been reported to be 17 to 28% and 7 to 9 months, respectively. Grade 3 or 4 hematologic and nonhematologic adverse events were observed in 57 to 76% (neutropenia) and 4 to 35% (vomiting), respectively (24, 25). In the present study with S-1 and cisplatin, the incidence of those adverse events seems to be lower than the above mentioned data. In addition, the antitumor mechanism is different from those agents. On the basis of these observations, we plan to conduct a randomized trial comparing the present combination chemotherapy with standard platinum-based two-drug combination chemotherapy regarding survival and the quality of life.

ACKNOWLEDGMENTS

We thank Brian Quinn for critical review and Yumiko Oshima for help in preparing the report.

REFERENCES

1. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 1993;53:4004–9.

2. Tatsumi K, Fukushima M, Shirasaka T, Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. Jpn J Cancer Res 1987;78:748–55.

3. Shirasaka T, Shimamato Y, Ohshimo H, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996;7:548–57.

4. van Groeningen CJ, Peters GJ, Schornagel JH, et al. Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. J Clin Oncol 2000;18:2772–9.

5. Yamada Y, Hamaguchi T, Goto M, et al. Plasma concentrations of 5-fluorouracil and F-beta-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. Br J Cancer 2003;89:816–20.

6. Kawahara M, Furuse K, Segawa Y, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 2001;85:939–43.

7. Fujii S, Kitano S, Ikenaka K, Shirasaka T. Effect of coadministration of uracil or cytosine on the anti-tumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann 1979;70:209–14.

8. Keicho N, Saijo N, Shinkai T, et al. Phase II study of UFT in patients with advanced non-small cell lung cancer. Jpn J Clin Oncol 1986;16: 143–6.

9. Ichinose Y, Takanashi N, Yano T, et al. A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable nonsmall cell lung cancer. Cancer (Phila) 1995;75:2677–80.

10. Ichinose Y, Yosimori K, Yoneda S, Kuba M, Kudoh S, Niitani H. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced nonsmall cell lung carcinoma: a multiinstitutional phase II trial. For the Japan UFT Lung Cancer Study Group. Cancer (Phila) 2000;88:318–23.

11. Saito J, Nakai Y, Saijo Y, et al. A phase II trial of oral UFT plus cisplatin (CDDP) in patients with non-small cell lung cancer (NSCLC). Lung Cancer 2001;31:285–93.

12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer (Phila) 1981;47:207–14.

13. Iyer L, Ratain MJ. 5-Fluorouracil pharmacokinetics: causes for variability and strategies for modulation in cancer chemotherapy. Cancer Investig 1999;17:494–506.

14. Meta-analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16:301–8.

15. Crawford J, O'Rourke M, Schiller JH, et al. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. J Clin Oncol 1996;14:2774–84.

16. Heim W, Wampler GL, Lokich JJ, et al. A study of infusional cisplatin and infusional fluorouracil for locally advanced or metastatic non-small-cell lung cancer: a Mid-Atlantic Oncology Program study. J Clin Oncol 1991;9:2162–6.

17. Decker DA, Drelichman A, Jacobs J, et al. Adjuvant chemotherapy with cis-diamminodichloroplatinum II and 120-hour infusion 5-fluorouracil in stage III and IV squamous cell carcinoma of the head and neck. Cancer (Phila) 1983;51:1353–5.

18. Kemeny N, Israel K, Niedzwiecki D, et al. Randomized study of continuous infusion fluorouracil versus fluorouracil plus cisplatin in patients with metastatic colorectal cancer. J Clin Oncol 1990;8:313–8.

19. Scanlon KJ, Newman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci USA 1986;83:8923–5.

20. Shirasaka T, Shimamoto Y, Ohshimo H, Saito H, Fukushima M. Metabolic basis of the synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo. Cancer Chemother Pharmacol 1993;32:167–72.

21. Kuroki M, Nakano S, Mitsugi K, et al. In vivo comparative therapeutic study of optimal administration of 5-fluorouracil and cisplatin using a newly established HST-1 human squamous-carcinoma cell line. Cancer Chemother Pharmacol 1992;29:273–6.

22. Koizumi W, Tanabe S, Saigenji K, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003;89:2207–12.

23. Klastersky J, Sculier JP, Ravez P, et al. A randomized study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced non-small-cell lung carcinoma. J Clin Oncol 1986;4:1780–6.

24. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210–8.

25. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.

ELSEVIER

European Journal of Radiology 52 (2004) 206–211

EJR
EUROPEAN JOURNAL OF RADIOLOGY

www.elsevier.com/locate/ejrad

Oblique approach of computed tomography guided needle biopsy using multiplanar reconstruction image by multidetector-row CT in lung cancer

Tatsuo Kimura [a,*], Nobuyuki Naka [a], Yoshiaki Minato [a], Yasushi Inoue [a], Takeshi Kimura [a], Hidenori Mawatari [a], Setsuko Yamauchi [a], Masanori Akira [b], Masaaki Kawahara [a]

[a] *Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, 1180 Nagasone-cho, Sakai-City, Osaka 591-8555, Japan*
[b] *Department of Radiology, National Kinki Central Hospital for Chest Diseases, 1180 Nagasone-cho, Sakai-City, Osaka 591-8555, Japan*

Received 12 December 2003; received in revised form 13 January 2004; accepted 15 January 2004

Abstract

The purpose of this study was to establish the technique of multiplanar reconstruction (MPR) with multidetector-row (MDR) computed tomography (CT) guided needle biopsy for the diagnosis to access very difficult lesions. The CT guided percutaneous biopsy are well-established methods to obtain cytological and histological material such as the peripheral tumors in lung cancer. Occasionally, the conventional CT cannot permit planning a trajectory to avoid passage through bones, avoidance of bullae, fissures or vessels. In addition, some lesions are situated in less favorable locations such as those in the costophrenic recess or close to the mediastinum. Rarely can we diagnose them. MPR with MDR-CT has recently become widely available with applications for thoracic lesions. MPR images have been used to evaluate the location of small peripheral lung nodules to the relation of bullaes, vessels, and costophrenic recess. To diagnose these lesions, the usefulness of MPR were evaluated for an planning of an oblique approach of CT guided needle biopsy. MPR images were reconstructed as a line from the needle entry point to the target lesion. The first oblique image applied as the direction of posterior–anterior and cranio-caudal axis, and the second oblique image applied as the direction of posterior–anterior and left–right.

Eleven out of 151 patients were required MPR technique to allow possible access to target, because of avoidance of bone and fissures in the needle pass or located in the costophrenic recess, between April 2001 and December 2002. The 5/11 patients were at the upper site (segment 1, 2 and 6) behind the scapula and ribs, 3/11 patients were at the lower lobe (segment 10) in the costophrenic recess, and 3/11 were middle lobe or segment 3 covered by the ribs and fissures. All the lesions except one were histologically diagnosed. Five patients were adenocarcinoma, and the other five patients were benign tumors. Pneumothorax occurred in one patient before we obtained the specimens. MPR guided needle biopsy with oblique approach was thought to be useful for diagnosis of very difficult thoracic lesions and would obviate an unnecessary surgical thoracoscopy.

Keywords: Multiplanar reconstruction; CT guided needle biopsy; Multidetector-row CT; Lung cancer

1. Introduction

The endoscopical bronchobiopsy and the percutaneous biopsy are today a well-established technique for the diagnosis of lung cancer, and indicate when the histological diagnosis can influence the therapeutic strategy. The endoscopical bronchobiopsy provide the answer to a great extent, however, peripheral tumors not visible on endobronchial examination are diagnosed less readily. The computed tomography (CT) guided percutaneous biopsy is also well-established methods to obtain cytological and histological material such as the peripheral tumors [1–6]. The CT guided biopsy is mainly indicated when the diagnosis cannot be established by bronchoscopic techniques. Percutaneous CT guided biopsy has an overall sensitivity of 70–100% for diagnosis of malignancy, most reports being in the 85–95% range [7]. The most common causes of false-negative are sampling error and inaccurate needle placement [8]. Other cases of false-negative

* Corresponding Author. Present address: Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. Tel.: +81-6-6645-3801; fax: +81-6-6645-3802.
E-mail address: kimutats@yo.rim.or.jp (T. Kimura).

0720-048X/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2004.01.007

are those which CT cannot permit planning a trajectory to avoid passage through bones, avoidance of bullae, fissures or vessels. Occasionally, the lesions are situated in less favorable locations such as those in the costophrenic recess or close to the mediastinum.

The spiral or helical CT imaging, with the ability to obtain a series of continuous images in 30 s during a single breath-hold, has shown promise in the evaluation of complex pathology. Spiral CT creates accurate volume data that can be viewed not only as trans-axial images, but also as multiplanar reconstructions (MPRs) (e.g. coronal, sagittal, or other user-defined oblique planes) [9–11]. Multidetector row (MDR) CT scanner allows for unprecedented speed for CT image acquisition. This acquired speed allows us depiction of the smaller volume of data on the oblique images. Furthermore, the use of MDR-CT significantly clarified the relation of lung tumor to vessels, bullae and pleura [11–13]. These thinner images can be reformatted into off-axis planes to produce unique anatomic displays that were not previously possible. To my knowledge, the idea of the oblique approach to lesions was described as early as 1976 by Greene [14]. However, the conventional CT scan needs a long time to describe the oblique.

The purpose of this study was to establish the oblique approach technique of MPR with MDR-CT guided needle biopsy for the diagnosis to access very difficult lesions. Those accesses may avoid bones, bullae, fissures and vessels, or may be able to access lesions located in the costophrenic recess or close to the mediastinum. These technical improvements of guidance may decrease the rate of biopsies technically impracticable, the rate of complications.

2. Materials and methods

All lesions were imaged on a CT scanner at a dose of 120 kVp, 100 mA. The CT scanner's (LightSpeed Plus; GE Medical Systems, Milwaukee, USA) detector configuration was 2.5 times 4.0 mm in the interspaced high-speed mode, in which four interspaced helical data sets are collected from four 1.25 mm detector rows. The high-speed mode is equivalent to pitch of 3, with the table speed set at 7.5 mm rotation. One rotation of the X-ray tube was 0.5 s. The MPR images were reconstructed and displayed from the transverse images of 15–20 sections (2.5 mm thick). All biopsies were performed with a 18-guage, needle length of 100 mm introducer needle (Hakko, Tokyo, Japan) and a 20-guage, needle length 160 mm core tissue biopsy needle (Bard, Covington, USA) to be used with Bard Magnum biopsy instrument (Bard, Covington, USA).

Oncologists and surgeons at clinical conferences primarily referred patients and the informed consent was obtained. Patients with a unique functional lung, severe cough, severe chronic obstructive pulmonary disease, cardiac insufficiency, or any other contradictions which were considered to be impossible to perform the biopsy, were excluded. Before the first CT scanning, a wire was placed on the skin as a marker on CT images. When the lesions are located in the costophrenic recess or close to the mediastinum, or any trajectory cannot avoid scapula, rib, bullae, or vessel on either breath exhalation or inhalation hold on axial scanning image, MPR images were constituted in order to select the favorable needle entry point. MPR images were reconstructed as a line from the favorable needle entry point to the target lesion. The first oblique image applied as the direction of posterior–anterior axis and cranio-caudal axis, and the second oblique image applied as the direction of posterior–anterior axis and left–right axis. The distances from the needle entry point to the lesion and pleura and the target, and the angle from cranio-caudal axis to considerable needle pass line was calculated (Fig. 1A) on the first oblique image. The distance from the needle entry point to the wire and the angle from left–right axis to needle passing line (Fig. 1B) on the second oblique image. Figs. 1–3 showed the case that the tumor was located at left upper lung at segments 1 + 2. This tumor was located just behind the rib, and faced on bullae. The patient was in prone position. Lesion size was measured along the maximum times minimum diameters. After the favorable needle entry point was marked on the skin, lidocaine 1% solution was used for local anesthesia.

Another two doctors were standing with a protractor at the side of and in front of the patient. They instructed the operator to adjust the direction of needle through the protractor. The guide needle was advanced through the skin to the margin of pleura with the patient's breathing suspended. The first oblique image applied as the direction of posterior–anterior axis and cranio-caudal axis (Fig. 2A). The second oblique

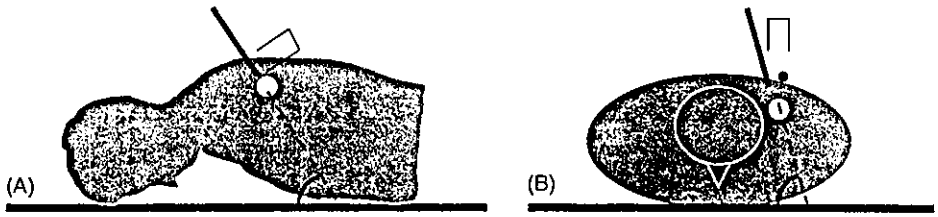

Fig. 1. The schemas of the body position, target lesion and needle direction. The white circle means the target, the black circle means the wire, and the line shows the direction of the needle. Panel A shows the distance from the needle entry point to the lesion and pleura, and the angle from cranio-caudal axis to considerable needle pass line. Panel B shows the distance from the needle entry point to the wire and the angle from left–right axis to needle passing line.

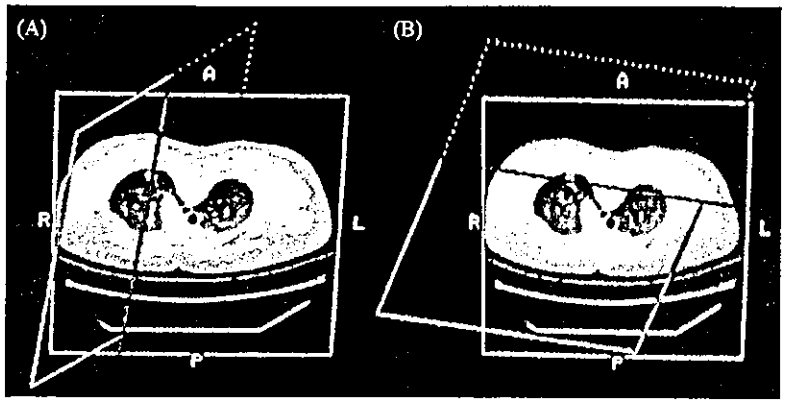

Fig. 2. (A) Induction image of a first oblique image applied as the plane of posterior–anterior axis and cranio-caudal axis. (B) Induction of a second oblique image reconstructed the plane of posterior–anterior and left–right axis.

image applied as the direction of posterior–anterior axis and left–right axis (Fig. 2B), A confirmatory helical acquisition was performed through the needle shaft to the target, and reconstructed into two MPR images. Fig. 3A showed the first oblique images. This image indicated the planes of MPR images corresponding to Fig. 2A. Fig. 3B as the second oblique image, corresponding to Fig. 2B. The inducer needle was adjusted by following the directions of another two doctors with protractors. The CT scanning time was about 30 s and the construction time of the MPR image was about 30 s.

The following technique was almost same as previously reported of CT guided core biopsy [1–3,5,15].

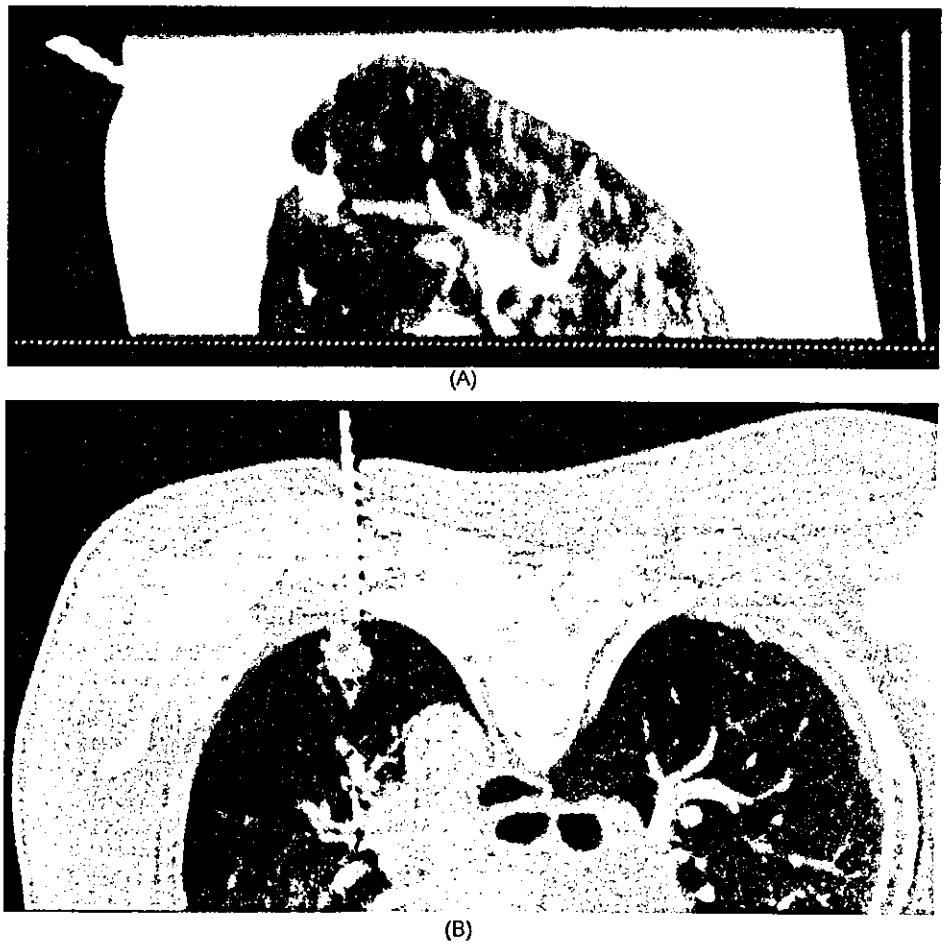

Fig. 3. (A) The first oblique image corresponding to the plane indicated Fig. 2A. (B) The second oblique image corresponding to the plane indicated Fig. 2B.

Briefly, Adjustments in needle position were then made and rechecked until the guide needle tip was immediately adjacent to the proximal edge of the lesion. The core tissue biopsy needle was inserted through the introducer needle and the biopsy system was fired. With a probable tumor, the biopsy was repeated until at least two samples were obtained. The specimens were placed into formalin solution until histological examination. With a suspected infectious illness, the needles were washed by saline for bacteriologic analysis. Each procedure was performed very carefully and one patient needs 30–60 min to finish all steps.

After removal of the biopsy needle, patients were placed in a puncture side-down position for 2 h. All patients had limited CT scans after biopsy to evaluate for the presence of a pneumothorax, when a severe pneumothorax was present, the patients were treated with placement of a chest tube. The next morning, all patients were examined by chest radiographs. Patients with enlarging pneumothoraces on serial chest radiographs or with symptomatic pneumothoraces were treated in the same way.

3. Results

From April 2001 to December 2002, there were 151 patients who underwent CT guided percutaneous lung biopsies at our institution. It was necessary in 11 out of 151 patients to use the MPR technique to access to target, with avoidance of bone and fissures in the needle pass. Table 1 summarizes the patient characteristics including gender, age, the lesion size, the distance from skin to lesion, the segment of each lesion, the patient position, diagnosis and complications. The 5/11 patients, including the case shown previously, were at the upper site (segments 1, 2 and 6) behind the scapula and ribs, 3/11 patients were at the lower lobe (segment 10) in the costophrenic recess, and 3/11 were middle lobe or segment 3 covered by the ribs and fissures. The biopsy was performed with 9/11 patients in prone position and 2/11 patients in supine position. All the lesions except one were histologically diagnosed. Five patients were adenocarcinoma, and the other five patients were benign tumors. Pneumothorax occurred in one patient before we obtained the specimens.

4. Discussion

Lung cancer continues to be the leading cause of cancer death in Japan and the US, with a chance of cure in a minor proportion of patients resected at an early stage. The theoretical advantage of CT for lung cancer screening is its ability to demonstrate small cancers, presumably at stage I [16,17]. The primary tumor size, stage, and were significant prognostic factors for survival [18,19].

Research at Mayo Clinic compared chest radiographs and sputum cytology every 4 months for 6 years against standard follow-up [17]. No overall reduction in mortality, but better survival for individuals in the intervention arm was found. Moreover, that report indicates that CT can be used for screening for lung cancer. Another study of The Early Lung Cancer Action Project group reported the usefulness of annual helical low-dose CT scanning compared with chest radiography in heavy smokers over the age of 60 years [16]. On low-dose CT, they detected small non-calcified nodules of lung cancer at an earlier stage, which are more curable. These kinds of screening are becoming more popular now. As it turned out, the population of tumors situated in the less favorable locations will be increasing. Preoperative diagnosis of a pulmonary nodule by CT biopsy would be necessary for them. The success of diagnosis by CT biopsy would obviate an unnecessary surgical thoracoscopy.

The real-time CT (CT fluoroscopy) was developed to overcome the limitations of conventional CT [20–22]. The methods of guided needle biopsies of the lung using the real-time CT (CT fluoroscopy) can allow real-time visualization of the needle tip or the site of the lesion. In addition, the total time is very short. Compared with CT fluoroscopy, the advantages of MPR guidance of lung biopsies include the following; our methods permit planning a trajectory with avoidance of bullae, fissures or vessels in oblique images. That approach to the lesion might be possible to select from any entry point from any direction. The radiation exposure to the operator

Table 1
Patient characteristics

Number	Gender	Age (years)	Size (mm)	Distance (mm)	Location	Position	Diagnosis	Complication
1	F	71	12 × 12	72	LtS1+2	Prone	Adenocarcinoma	None
2	F	69	20 × 10	52	LtS10	Prone	Adenocarcinoma	None
3	M	47	15 × 10	50	LtS1+2	Prone	Adenocarcinoma	None
4	F	75	20 × 10	16	LtS3	Supine	Adenocarcinoma	None
5	F	60	10 × 10	30	RtS6	Prone	Eosinophilic granuloma	None
6	M	72	30 × 30	62	LtS1+2	Prone	Silicosis	None
7	M	61	10 × 10	46	RtS10	Prone	Eosinophilic granuloma	None
8	M	54	10 × 7	20	RtS3	Supine	Solitary fibrous tumor	None
9	F	53	30 × 10	41	RtS4	Prone	Adenocarcinoma	None
10	M	53	10 × 10	57	RtS2	Prone	No diagnosis	Pneumothorax
11	M	54	8 × 8	46	RtS10	Prone	Tuberculoma	None

is negligible. In our institute, these MPR images were reconstructed from the transverse images of 15–20 sections (2.5 mm thick). The images were not so sharp, but enough clear to evaluate the needle from pleura and target lesion in short time. In the future, CT fluoroscopy technique will combine the advantage of MPR guidance. Further technical improvements of guidance may decrease the rate of biopsies technically impracticable, the rate of complications.

A major complication of a CT guided lung biopsy is the development of a pneumothorax and bleeding. Pneumothorax has been reported from 0 to 61%, 20% in most recent large series and the rate of pneumothoraces requiring treatment with chest tube varies from 1.6 to 17% [7]. Unfortunately, we had one patient whom we could not obtain the specimen because of the pneumothorax. Essentially, the oblique approach needs longer insertion from needle entry point to pleura than that of perpendicular approach. In the oblique approach, the direction of needle is very important. The wrong direction of needle approach cause unexpected complications such as pneumothorax. In addition, the pulmonary nodules move with respiration. The patient's cooperation is thus indispensable to perform CT guided needle biopsies. Slight movement or unstable breath holding during the biopsy renders the initial localization of the lesion inaccurate, making the needle biopsy more difficult, particularly with small lesions [23]. In this regard, as described by Moore, we also recognize patient cooperation to be one of the most important factors necessary for a successful procedure [4].

Previous studies have reported accuracy for CT guided biopsy is related to the size of lesions [1,2,5,15]. In my knowledge, there were few reports that described the relation to the location of tumor and accuracy, except for those [23,24]. In my opinion, the location may affect the success of the biopsy procedures. A limitation of our study is that it was small population and subject to patient selection bias. However, the goal of our study was to improve the technique of CT guidance and increase accuracy and decrease false-negative cases.

Here we reported just technical aspects in this study, and we proved the possibility of oblique needle biopsy with safety and speedy using MDR-CT. It is concluded from present study that MPR guided lung core biopsy is a method of choice for lesions in difficult positions and thought to be useful in the preoperative assessment. It has widened the scope of lesions in unfavorable locations to be targeted accurately. Future studies should include an increased sample size and compare sensitivity and accuracy to other techniques.

Acknowledgements

The authors thank Chisa Hamaguchi, Isamu Tanaka, Takeshi Nakamura, Yutaka Fujimoto and Shinichi Matsuoka for their technical advices, and thank Christopher M. Mahaffey for his thoughtful grammatical check of this manuscript.

References

[1] Haramati LB. CT-guided automated needle biopsy of the chest. AJR Am J Roentgenol 1995;165(1):53–5.
[2] Klein JS, Salomon G, Stewart EA. Transthoracic needle biopsy with a coaxially placed 20-gauge automated cutting needle: results in 122 patients. Radiology 1996;198(3):715–20.
[3] Westcott JL, Rao N, Colley DP. Transthoracic needle biopsy of small pulmonary nodules. Radiology 1997;202(1):97–103.
[4] Moore EH. Technical aspects of needle aspiration lung biopsy: a personal perspective. Radiology 1998;208(2):303–18.
[5] Lucidarme O, Howarth N, Finet JF, Grenier PA. Intrapulmonary lesions: percutaneous automated biopsy with a detachable, 18-gauge, coaxial cutting needle. Radiology 1998;207(3):759–65.
[6] Lopez Hanninen E, Vogl TJ, Ricke J, Felix R. CT-guided percutaneous core biopsies of pulmonary lesions. Diagnostic accuracy, complications and therapeutic impact. Acta Radiol 2001;42(2):151–5.
[7] Klein JS, Zarka MA. Transthoracic needle biopsy. Radiol Clin North Am 2000;38(2):235–66, vii.
[8] Yankelevitz DF, Vazquez M, Henschke CI. Special techniques in transthoracic needle biopsy of pulmonary nodules. Radiol Clin North Am 2000;38(2):267–79.
[9] Johnson CD. Pancreatic carcinoma: developing a protocol for multi-detector row CT. Radiology 2001;220(1):3–4.
[10] Ghaye B, Szapiro D, Mastora I, Delannoy V, Duhamel A, Remy J, et al. Peripheral pulmonary arteries: how far in the lung does multi-detector row spiral CT allow analysis. Radiology 2001;219(3):629–36.
[11] Lawler LP, Fishman EK. Multi-detector row CT of thoracic disease with emphasis on 3D volume rendering and CT angiography. Radiographics 2001;21(5):1257–73.
[12] Raptopoulos V, Boiselle PM. Multi-detector row spiral CT pulmonary angiography: comparison with single-detector row spiral CT. Radiology 2001;221(3):606–13.
[13] Padhani AR, Fishman EK, Heitmiller RF, Wang KP, Wheeler JH, Kuhlman JE. Multiplanar display of spiral CT data of the pulmonary hila in patients with lung cancer. Preliminary observations. Clin Imaging 1995;19(4):252–7.
[14] Greene R. Fluoroscopic axialography: clinical applications in thoracic disease. Radiology 1976;121(3 Pt 1):527–31.
[15] Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. AJR Am J Roentgenol 2000;175(1):239–43.
[16] Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354(9173):99–105.
[17] Marcus PM, Bergstralh EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000;92(16):1308–16.
[18] Dash BK, Tripathy SK. Comparison of accuracy and safety of computed tomography guided and unguided transthoracic fine needle aspiration biopsy in diagnosis of lung lesions. J Assoc Physicians India 2001;49:626–9.
[19] Kimura T, Kudoh S, Hirata K, Takifuji N, Negoro S, Yoshikawa J. Prognostic factors in elderly patients with unresectable non-small cell lung cancer. Anticancer Res 2001;21(2B):1379–83.
[20] Katada K, Kato R, Anno H, Ogura Y, Koga S, Ida Y, et al. Guidance with real-time CT fluoroscopy: early clinical experience. Radiology 1996;200(3):851–6.

[21] Kirchner J, Kickuth R, Laufer U, Schilling EM, Adams S, Liermann D. CT fluoroscopy-assisted puncture of thoracic and abdominal masses: a randomized trial. Clin Radiol 2002;57(3):188–92.
[22] Muehlstaedt M, Bruening R, Diebold J, Mueller A, Helmberger T, Reiser M. CT/fluoroscopy-guided transthoracic needle biopsy: sensitivity and complication rate in 98 procedures. J Comput Assist Tomogr 2002;26(2):191–6.
[23] Laurent F, Montaudon M, Latrabe V, Begueret H. Percutaneous biopsy in lung cancer. Eur J Radiol 2003;45(1):60–8.
[24] vanSonnenberg E, Casola G, Ho M, Neff CC, Varney RR, Wittich GR, et al. Difficult thoracic lesions: CT-guided biopsy experience in 150 cases. Radiology 1988;167(2):457–61.

Screening for lung cancer

Masaaki Kawahara

Purpose of review

With the development of newer forms of technology such as low-dose spiral computed tomography, there has been a resurgent interest in screening for lung cancer. The purpose of this review is to highlight recent advances in screening for lung cancer. Articles published since September 2002 are reviewed here.

Recent findings

More frequent screenings (every 4 or 6 months) showed increased mortality from lung cancer, compared with annual screening. A mass screening conducted in 1990 was effective in a case-control study. The results of lung cancer screening by low-dose spiral computed tomography were reported from the Milan group and the Mayo Clinic. Computed tomography depicted peripheral early lung cancer, especially adenocarcinoma. These results are consistent with previous reports from other groups. Screening with imaging becomes more sensitive with automated computerized methods.

Summary

A high percentage of stage IA lung cancers were detected by screening with low-dose helical computed tomography. The characteristics of the nodules detected by low-dose spiral computed tomography have been clarified. There have been many controversial discussions about cost effectiveness and overdiagnosis. There is still no evidence that screening tests reduce the rate of cancer-specific mortality. Several studies of screening for lung cancer are under way.

Keywords

low-dose computed tomography, lung cancer, screening, overdiagnosis, early stage

Curr Opin Oncol 16:141–145.

Department of Internal Medicine, National Kinki Central Hospital for Chest Disease, Osaka, Japan

Correspondence to Masaaki Kawahara, National Kinki Central Hospital for Chest Diseases, 1180 Nagasone, Sakai, Osaka, 591-8555, Japan
Tel: +81 72 252 3021; fax: +81 72 250 4034;
e-mail: kawaharam@kch.hosp.go.jp

Current Opinion in Oncology 2004, 16:141–145

Abbreviations

ELCAP	Early Lung Cancer Action Project
FDG	fluorodeoxyglucose
PET	positron emission tomography

1040-8746

Introduction

Lung cancer is the leading cause of death from cancer in many industrialized countries [1]. The overall 6-year survival rates remain at approximately 15%, and most patients at diagnosis have advanced disease.

The individual risk of lung cancer depends almost exclusively on exposure to inhaled carcinogens such as cigarette smoke. Therefore, primary prevention of lung cancer is to reduce the exposure to these carcinogens. Secondary prevention aims at diagnosis of preclinical or early stages of lung cancer, particularly non–small-cell lung cancer. Early detection is less efficient and more costly than primary prevention but can be made available for people who have already been exposed to carcinogens. Success in screening for cancer depends on several basic assumptions: there must be effective treatment at the preclinical stage that can reduce mortality in the screened group as compared with the unscreened group. The prevalence, specificity, sensitivity, accessibility, cost, and associated morbidity of the screening method must also be reasonable.

Previous studies using chest radiography and sputum cytology failed to reduce disease-specific mortality [2–5]. This review of screening for lung cancer is based mainly on data published since September 2003.

Screening with sputum cytology and chest radiography

Manser *et al.* [6••] reported a first systemic review of controlled trials to determine whether screening for lung cancer using sputum examination or chest radiography or CT reduces lung cancer mortality. This review included 245,610 subjects. More frequent screening (every 4 or 6 months) (RR 1.11, 95% CI 1.00–1.23) showed increased mortality from lung cancer compared with less frequent screening. In general, the harm associated with screening was poorly reported. Recently used spiral CT has not been incorporated in this study.

Sagawa *et al.* [7•] reported that the smoking adjusted odds ratio for those screened by sputum cytology and chest radiography *versus* those screened by chest radiography only was 0.63, but not significant. They also re-evaluated the efficacy of mass screening for lung cancer done in the 1990s [8•,9–12]. In a matched case-control study, the smoking-adjusted odds ratio in screened persons *versus* nonscreened persons within 12 months of pooled analysis was 0.56 (95% CI 0.48–0.65) with signifi-

cance. However, those authors admitted the existence of some confounding factors. All screening case-control studies are fraught with bias, and this is no exception [13•]. We must await an ongoing prostate, lung, colorectal, and ovarian trial funded by the National Cancer Institute and designed to evaluate the impact of annual chest radiography screening on lung cancer mortality [14].

Screening by use of computed tomography with or without positron emission tomography

Studies using low-dose CT for screening suggest that lung cancer can be detected at an earlier stage and with higher sensitivity than with chest radiography [15–17]. The fact that almost all screen-detected lung cancers were stage I and were successfully resectable led investigators at the Early Lung Cancer Action Project (ELCAP) to cast doubt on the necessity of randomized studies to establish the survival benefit of this screening approach [18]. Swensen *et al.* [19••] reported the results of the Mayo Clinic experience through 2001, including the results from the baseline prevalence and first two annual (incidence) CT examinations in 1520 participants aged 50 years or older who had smoked 20 pack-years or more. Two years after baseline CT screening, 40 cases of lung cancers were diagnosed: 26 at prevalence CT examination and 10 at subsequent incidence CT examination. CT alone depicted 36 cases; 93% of the lung cancer were stage I. Lately, those authors have identified 56 lung cancers (29 prevalence, 23 incidence, and 4 interval [20]. These results are consistent with those of the study by Sobue *et al.* [21] in which 36 lung cancers (14 prevalence, 22 incidence) were found in 1611 participants. In this Anti-Lung Cancer Association project, participants were invited to repeat the same screening twice a year.

The 2-year results of a screening trial for lung cancer in 1035 heavy smokers were reported by Pastorino *et al.* [22••]. These workers of the Milan group used low-dose CT to detect small pulmonary nodules and a diagnostic algorithm, including positron emission tomography (PET) and contrast-enhanced CT, to classify nodules as most likely benign or malignant. They reported a prevalence of 1.1% (11 cancers) and an incidence of 1.1% (11 cancers after 12 months). This study aimed to diagnose malignancy faster by including PET in the diagnostic algorithm. This study adds an important aspect to the field of lung cancer screening with low-dose CT: simplification of the diagnostic algorithm for nodule classification. More data are required to define the ideal algorithm.

In any study, the rate of detection of benign nodules is still high. The selection of the optimal target population is very important. Van Klaveren *et al.* [23••] recommend the inclusion of current smokers or ex-smokers (<5 years) with a smoking history of at least 30 years and an average consumption of at least 20 cigarettes a day.

As an ongoing trial, the National Cancer Institute [24] has launched a study to determine whether screening current and former smokers with spiral CT or chest radiography reduces their risk of dying of lung cancer. This study, called the National Lung Cancer Screening Trial, will enroll 50,000 persons aged 55 to 74 years at 30 sites throughout the United States. Patients in both screening groups will be screened once a year for 3 years, and all participants will be monitored until 2009. To look for biomarkers for early detection of lung cancer, the University of Colorado Specialized Program of Research Excellence (SPORE trial) conducted a cohort study of subjects at high risk for lung cancer (smoking history of ≥30 pack-years and chronic obstructive pulmonary disease defined by spirometry) [25]. McWilliams *et al.* conducted a pilot study that used the combined techniques of automated quantitative image cytometry (AQC) of sputum cells, autofluorescence bronchoscopy, and spiral CT [26]. AQC improved the detection rate of lung cancer from 1.8 to 3.1%.

Pulmonary nodules

Karabulut *et al.* [27] compared low-dose CT with standard CT in the evaluation of pulmonary nodules. This comparison was prospectively done in the same patients. There were no statistically significant differences in the number of nodules detected at standard CT or low-dose CT.

Li *et al.* [28] studied the differences in the appearance of the cancers in nonsmokers *versus* smokers in Japan. Most of the lung cancers in nonsmokers were slow-growing adenocarcinomas appearing as faint ground-glass opacities on CT, whereas rapidly growing cancers appearing as solid nodules were more commonly seen in smokers.

The detection rate for lung cancer was 1.1% for both nonsmokers (45 of 4,251) and smokers (39 of 3596). The prevalence of well-differentiated adenocarcinomas was greater in nonsmokers (88%, 22 of 25) than in smokers (29%, 4 of 14) ($P < 0.001$). The prevalence and incidence of pathologic stage IA disease were greater in nonsmokers than in smokers (92% [22 of 24] *vs* 58% [7 of 12] and 100% [19 of 19] *vs* 70% [14 of 20], respectively) (both $P < 0.05$). The mean size of the tumors in the nonsmokers (12.4 mm) was smaller than in smokers (18.2 mm) ($P < 0.001$). The percentage of cancers categorized as pure or mixed ground-glass opacity (86%, 38 of 44) on CT was greater in nonsmokers than in smokers (46%, 16 of 35) ($P < 0.001$). The authors included nonsmokers as well as smokers in their screening. Henschke *et al.* [29] reported that the malignancy rate was significantly higher for part-solid nodules than for either solid ($P = 0.004$) or nonsolid nodules ($P = 0.03$). The malignancy

type in the part-solid or nonsolid nodules was predominantly bronchioloalveolar carcinoma or adenocarcinoma with bronchioloalveolar features, contrasting with other subtypes of adenocarcinoma found in the solid nodules ($P = 0.0001$). At annual repeat screenings, only 30 instances of positive test results have been obtained; 7 of these involved part-solid or nonsolid nodules. The morphology of the nodules needs to be further classified.

Armato *et al.* [30] evaluated the performance of a fully automated computerized method for the detection of lung nodules in CT scans in the identification of lung cancers that may be missed during visual interpretation. Using this method, Armato *et al.* [32] reported that a large fraction of missed cancers (84%, 32 of 38) in a database of low-dose CT scans were detected correctly. This may help reduce the burden on the visual interpreter.

Aoyama *et al.* [32] reported that the automated method helped radiologists eliminate many benign nodules in a lung cancer screening program with low-dose CT. With a large base of 489 nodules, the performance of the automated computerized scheme with multiple slices of nodule images for determination of the likelihood measure of malignancy was greater than that with a single slice of nodule images. There was an improvement in distinguishing benign from malignant nodules when this method was used, compared with the results obtained by radiologists alone.

Ford *et al.* [33] reported on the adherence of screening. Statistically significant predictors of nonadherence by multivariate results were false positive cases with current or past smoking status. Additional predictors were being African American ($P < 0.01$), being female ($P < 0.001$), and having a high school education or less ($P < 0.01$). False positive results had a stronger effect on nonadherence among ever-smokers than among never-smokers.

Overdiagnosis represents a subclinical condition that would not have produced signs or symptoms before the individual died of other causes [34]. It may cause the person being screened to worry for months or years about having cancer.

Yankelevitz *et al.* [35] calculated the doubling times of stage I cancers detected by the Mayo Lung Project (MLP) and Memorial Sloan-Kettering Cancer Center (MSK) to estimate the frequency of overdiagnosis. The median doubling times were 101 days in the MLP and 144 days in the MSK. Only 5% had doubling times exceeding 400 days; 10% exceeded 300 days. The ELCAP group contradicted the idea that screening in the MLP with chest radiography led to a high proportion of overdiagnosis among diagnoses of early-stage lung carcinoma [36].

Kashiwabara *et al.* [37] evaluated the outcome in 45 patients with lung cancer found on lung cancer mass screening roentgenograms, but who did not subsequently consult a doctor. A 1-year delay in treatment itself affected the outcome. In their study, the tumor sizes in the delayed consultation group were 10 to 20 mm in 4 patients and greater than 20 mm in 41 patients, and there were no patients with tumor sizes less than 10 mm. This may not serve as a reference of small nodules less than 10 mm tumor.

Li *et al.* [38•] also showed that lung cancers were missed at low-dose CT screening in a general population in Nagano, Japan. All missed cancers were intrapulmonary, and 28 (88%) were stage IA. All 20 detection errors occurred in cases of adenocarcinoma, 17 (85%) of which were well-differentiated tumors and 11 (55%) of which were in nonsmoking women. These lung cancers were very subtle and appeared as small faint nodules, overlapping normal structures, or opacities in a complex background of other disease such as tuberculosis, emphysema, or lung fibrosis. This was the first study on characteristics of lung cancers missed at CT screening in a general population, including nonsmokers and women.

Takashima *et al.* [39] in Nagano, Japan, showed the reliability of high-resolution CT features of benign lesions, which were small solitary pulmonary nodules (≤1 cm) detected by population-based CT screening for lung cancer. Takashima *et al.* [40] advocated the usefulness of follow-up CT with a combination of findings on initial and follow-up CT to differentiate benign and malignant nodules.

A serious concern has been raised that the better our methods of detection become, the more overdiagnosis of lung cancer we will have. Ost *et al.* [41] briefly reviewed the clinical problem with the solitary pulmonary nodule.

Cost-effectiveness study

Lung cancer screening with low-dose CT is likely to be cost effective if the screening process can detect more than 50% of cancers at a localized stage [42].

Preliminary results of baseline screening were released by Wisnivesky *et al.* [43]. Data from the ELCAP were incorporated into a decision analysis model comparing low-dose CT scan screening of high-risk individuals (*ie* those ≥60 years old with at least 10 pack-years of cigarette smoking and no other malignancies) to observation without screening. The incremental cost-effectiveness ratio of a single baseline low-dose CT scan was $2500 per year of life saved. In the base-case analysis, screening would be expected to increase survival by 0.1 year at an incremental cost of approximately $230. The authors concluded that a baseline low-dose CT scan for lung cancer screening is potentially highly cost-effective.

By contrast, Mahadevia *et al.* [44••] estimated the potential benefits, harms, and cost-effectiveness of lung cancer screening with helical CT in various efficacy scenarios. They compared annual helical CT screening with no screening for hypothetical cohorts of 100,000 current, quitting, and former heavy smokers, aged 60 years, of whom 55% were men. In multiway sensitivity analyses, a program screening current smokers was $42,500 per quality adjusted life years (QALY) gained if extremely favorable estimates were used for all of the influential parameters simultaneously. The authors concluded that given the current uncertainty of benefits, the harms from invasive testing, and the high costs associated with screening, direct-to-consumer marketing of helical CT is not advisable. Future advancements in lung cancer diagnosis and treatment could make their result out of date.

Comber *et al.* [45]. studied the impact of quantitative contrast-enhanced CT (QECT) on the cost-effectiveness of fluorodeoxyglucose (FDG)-PET. The QECT strategy incurred the least cost ($5560/patient), but the QECT+PET strategy was the most cost effective (incremental cost-to-accuracy ratio $12059/patient). The problem was the low specificity of QECT: they assumed it to be 0.58. This technique awaits further validation.

Centrally located lung cancer

The sensitivity of bronchoscopic detection of early lung cancer depends on the size of the nodule, the site of the lesion, and the prevalence in the study population.

The focus of screening seems to have moved toward peripheral lung cancer. However, detection of centrally located lung cancer is still important. Recent developments in the detection of preinvasive lesions of the large airways by fluorescence bronchoscopy have been reviewed by Banerjee *et al.* [46•]. Sutedja [47•] recently reviewed new techniques such as fluorescence bronchoscopy and innovative sputum screening.

Effect of screening on smoking habit

Schnoll *et al.* [48] reported psychologic issues related to the use of spiral CT. Greater motivation of female smokers to quit smoking was related to greater age, lower nicotine addiction, fewer health symptoms, and higher quitting self-efficacy and pros of quitting. In their study, 16% of enrollees quit smoking after screening. Schnoll *et al.* [49] also showed that 59% of smokers were interested in smoking cessation counseling, with screening.

Several excellent reviews, comments, or editorials on the screening for lung cancer have been published recently [50•–58•].

Conclusion

Although low-dose CT can depict early-stage lung cancers, the rate of benign nodule detection is still high. Screening with imaging has become more sophisticated. There is still no evidence that screening tests reduce the rate of cancer-specific mortality. Its efficiency depends on many factors such as the advancement of diagnostic methods, financial cost, and psychologic effect as well as the prevalence of curable lung cancer in the screened population.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 Jemal A, Murray T, Samuels A, et al.: Cancer statistics, 2003. CA Cancer J Clin 2003, 53:5–26.

2 Kubik AK, Parkin DM, Zatloukal P: Czech study on lung cancer screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. Cancer 2000, 89:2363–2368.

3 Fontana RS, Sanderson DR, Miller WE, et al.: The Mayo Lung Project: preliminary report of "early cancer detection" phase. Cancer 1972, 30:1373–1382.

4 Melamed MR: Lung cancer screening results in the National Cancer Institute New York study. Cancer 2000, 89:2356–2362.

5 Levin ML, Tockman MS, Frost JK, et al.: Lung cancer mortality in males screened by chest X-ray and cytologic sputum examination: a preliminary report. Recent Results Cancer Res 1982, 82:138–146.

6 •• Manser RL, Irving LB, Byrnes G, et al.: Screening for lung cancer: a systematic review and meta-analysis of controlled trials. Thorax 2003, 58:784–789.
First systematic review of lung cancer screening. More frequent screening (4- to 6-monthly) increased mortality from lung cancer.

7 Sagawa M, Saito Y, Sato M, et al.: The efficacy of sputum cytology in mass screening program for early detection of lung cancer. Anticancer Res 2003, 23:597–600.

8 • Sagawa M, Nakayama T, Tsukada H, et al.: The efficacy of lung cancer screening conducted in 1990s: four case-control studies in Japan. Lung Cancer 2003, 41:29–36.
Efficacy of mass screening for lung cancer is demonstrated by case-control study.

9 Nakayama T, Baba T, Suzuki T, et al.: An evaluation of chest X-ray screening for lung cancer in Gunma Prefecture, Japan: a population-based case-control study. Eur J Cancer 2002, 38:1380–1387.

10 Tsukada H, Kurita Y, Yokoyama A, et al.: An evaluation of screening for lung cancer in Niigata Prefecture, Japan: a population-based case-control study. Br J Cancer 2001, 85:1326–1331.

11 Sagawa M, Tsubono Y, Saito Y, et al.: A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. Cancer 2001, 92:588–594.

12 Nishii K, Ueoka H, Kiura K, et al.: A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer 2001, 34:325–332.

13 • Marcus PM: Conflicting evidence in lung cancer screening: randomized controlled trials versus case-control studies. Lung Cancer 2003, 41:37–39.
This article is a good commentary on randomized controlled trials and case-controlled studies.

14 Gohagan JK, Prorok PC, Hayes RB, et al.: The prostate, lung, colorectal and ovarian (PLCO) cancer screening trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 2000, 21:251S–272S.

15 Henschke CI, McCauley DI, Yankelevitz DF, et al.: Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999, 354:99–105.

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

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

18 Miettinen OS, Yankelevitz DF, Henschke CI: Evaluation of screening for a cancer: annotated catechism of the gold standard creed. J Eval Clin Pract 2003, 9:145–150.

19 •• Swensen SJ, Jett JR, Hartman TE, et al.: Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003, 226:756–761.
Description of the Mayo Clinic experience using low-dose CT.

20 Swensen SJ, Jett JR, Midthun DE, et al.: Computed tomographic screening for lung cancer: home run or foul ball? Mayo Clin Proc 2003, 78:1187–1188.

21 Sobue T, Moriyama N, Kaneko M, et al.: Screening for lung cancer with low-dose helical computed tomography: Anti-lung Cancer Association Project. J Clin Oncol 2002, 20:911–920.

22 •• Pastorino U, Bellomi M, Landoni C, et al.: Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003, 362:593–597.
A study of the Milan group: low-dose spiral CT combined with selective use of PET can effectively detect early lung cancer.

23 •• van Klaveren RJ, de Koning HJ, Mulshine J, et al.: Lung cancer screening by spiral CT: what is the optimal target population for screening trials? Lung Cancer 2002, 38:243–252.
Good criteria considering future treatment if lung cancer is detected.

24 Recruitment begins for lung cancer screening trial. J Natl Cancer Inst 2002, 94:1603.

25 Hirsch FR, Prindiville SA, Byers T, et al.: Sputum cytology as a marker of risk for lung cancer–preliminary results from the University of Colorado High Risk Cohort Study. Proc Am Soc Clin Oncol 2002, 21:301a.

26 McWilliams A, Mayo J, MacDonald S, et al.: Lung cancer screening: a different paradigm. Am J Respir Crit Care Med 2003, 25:25.

27 Karabulut N, Toru M, Gelebek V, et al.: Comparison of low-dose and standard-dose helical CT in the evaluation of pulmonary nodules. Eur Radiol 2002, 12:2764–2769.

28 Li F, Sone S, Abe H, et al.: Low-dose computed tomography screening for lung cancer in a general population: characteristics of cancer in non-smokers versus smokers. Acad Radiol 2003, 10:1013–1020.

29 Henschke CI, Yankelevitz DF, Mirtcheva R, et al.: CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002, 178:1053–1057.

30 Armato SG 3rd, Altman MB, Wilkie J, et al.: Automated lung nodule classification following automated nodule detection on CT: a serial approach. Med Phys 2003, 30:1188–1197.

31 Armato SG 3rd, Li F, Giger ML, et al.: Lung cancer: performance of automated lung nodule detection applied to cancers missed in a CT screening program. Radiology 2002, 225:685–692.

32 Aoyama M, Li Q, Katsuragawa S, et al.: Computerized scheme for determination of the likelihood measure of malignancy for pulmonary nodules on low-dose CT images. Med Phys 2003, 30:387–394.

33 Ford ME, Havstad SL, Flickinger L, et al. Examining the effects of false positive lung cancer screening results on subsequent lung cancer screening adherence. Cancer Epidemiol Biomarkers Prev 2003, 12:28–33.

34 Black WC: Overdiagnosis: an underrecognized cause of confusion and harm in cancer screening. J Natl Cancer Inst 2000, 92:1280–1282.

35 Yankelevitz DF, Kostis WJ, Henschke CI, et al.: Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. Cancer 2003, 97:1271–1275.

36 Marcus PM, Bergstralh EJ, Fagerstrom RM, et al.: Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000, 92:1308–1316.

37 Kashiwabara K, Koshi S, Itonaga K, et al.: Outcome in patients with lung cancer found on lung cancer mass screening roentgenograms, but who did not subsequently consult a doctor. Lung Cancer 2003, 40:67–72.

38 • Li F, Sone S, Abe H, et al.: Lung cancers missed at low-dose helical CT screening in a general population: comparison of clinical, histopathologic, and imaging findings. Radiology 2002, 225:673–683.
Description of characteristics of lung cancer missed at CT screening in a general population, including nonsmokers and women.

39 Takashima S, Sone S, Li F, et al.: Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening for lung cancer: reliable high-resolution CT features of benign lesions. AJR Am J Roentgenol 2003, 180:955–964.

40 Takashima S, Sone S, Li F, et al.: Indeterminate solitary pulmonary nodules revealed at population-based CT screening of the lung: using first follow-up diagnostic CT to differentiate benign and malignant lesions. AJR Am J Roentgenol 2003, 180:1255–1263.

41 Ost D, Fein AM, Feinsilver SH: Clinical practice: the solitary pulmonary nodule. N Engl J Med 2003, 348:2535–2542.

42 Chirikos TN, Hazelton T, Tockman M, et al.: Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. Chest 2002, 121:1507–1514.

43 Wisnivesky JP, Mushlin AI, Sicherman N, et al. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest 2003, 124:614–621.

44 •• Mahadevia PJ, Fleisher LA, Frick KD, et al.: Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. JAMA 2003, 289:313–322.
Good insight into the important factors influencing screening efficacy and the potential economic and safety consequences of screening programs.

45 Comber LA, Keith CJ, Griffiths M, et al. Solitary pulmonary nodules: impact of quantitative contrast-enhanced CT on the cost-effectiveness of FDG-PET. Clin Radiol 2003, 58:706–711.

46 • Banerjee AK, Rabbitts PH, George J: Lung cancer. 3: Fluorescence bronchoscopy: clinical dilemmas and research opportunities. Thorax 2003, 58:266–271.
Review of fluorescence bronchoscopy.

47 • Sutedja G: New techniques for early detection of lung cancer. Eur Respir J Suppl 2003, 39:57s–66s.
Introduction of new techniques such as autofluorescence bronchoscopy and innovative sputum screening.

48 Schnoll RA, Miller SM, Unger M, et al.: Characteristics of female smokers attending a lung cancer screening program: a pilot study with implications for program development. Lung Cancer 2002, 37:257–265.

49 Schnoll RA, Bradley P, Miller SM, et al.: Psychological issues related to the use of spiral CT for lung cancer early detection. Lung Cancer 2003, 39:315–325.

50 • Mulshine JL: Screening for lung cancer: in pursuit of pre-metastatic disease. Nat Rev Cancer 2003, 3:65–73.
Introduction to more sensitive imaging tools for screening.

51 • Bach PB, Niewoehner DE, Black WC: Screening for lung cancer: the guidelines. Chest 2003, 123:83S–88S.
Guidelines for lung cancer screening.

52 • Bach PB, Kelley MJ, Tate RC, et al.: Screening for lung cancer: a review of the current literature. Chest 2003, 123:72S–82S.
Review of the current literature.

53 • Gould MK, Sanders GD, Barnett PG, et al.: Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. Ann Intern Med 2003, 138:724–735.
The use of FDG-PET in relation to pretest probability of lung cancer and CT.

54 • Baldwin J: New study questions marketing of spiral CT scanning to consumers. J Natl Cancer Inst 2003, 95:507–509.
News about marketing of spiral CT scanning to consumers.

55 • Berlin L: Liability of performing CT screening for coronary artery disease and lung cancer. AJR Am J Roentgenol 2002, 179:837–842.
This report includes the radiologist's view.

56 • Valle RP, Chavany C, Zhukov TA, et al.: New approaches for biomarker discovery in lung cancer. Expert Rev Mol Diagn 2003, 3:55–67.
Review of biomarkers in lung cancer and introduction of antibiomix approach.

57 • Bepler G, Goodridge Carney D, Djulbegovic B, et al.: A systematic review and lessons learned from early lung cancer detection trials using low-dose computed tomography of the chest. Cancer Control 2003, 10:306–314.
Many detailed tables are included in this review.

58 • Swensen SJ: CT screening for lung cancer. AJR Am J Roentgenol 2002, 179:833–836.
Perspective on CT screening.

Lung Cancer (2004) 43, 301–307

ELSEVIER

LUNG CANCER

IASLC

www.elsevier.com/locate/lungcan

Hypercalcemia–leukocytosis syndrome associated with lung cancer

Akio Hiraki[a,*], Hiroshi Ueoka[a], Ichiro Takata[b], Kenichi Gemba[a], Akihiro Bessho[a], Yoshihiko Segawa[b], Katsuyuki Kiura[a], Kenji Eguchi[b], Toshiyuki Yoneda[c,d], Mitsune Tanimoto[a], Mine Harada[a]

[a] *Department of Medicine (II), Okayama University Medical School, Okayama, Japan*
[b] *Department of Medicine, National Shikoku Cancer Center, Matsuyama, Ehime, Japan*
[c] *Department of Biochemistry, Faculty of Dentistry, Osaka University, Suita, Osaka, Japan*
[d] *Department of Medicine, Division of Endocrinology and Metabolism, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*

Received 24 March 2003; received in revised form 26 August 2003; accepted 2 September 2003

KEYWORDS
Paraneoplastic syndrome;
Lung cancer;
Hypercalcemia;
Leukocytosis;
Prognosis

Summary Hypercalcemia and leukocytosis are two of the most common paraneoplastic syndromes associated with various malignancies. Of note, concomitant manifestation of hypercalcemia and leukocytosis are occasionally observed in the same cancer patients. However, the relationship between these two paraneoplastic syndromes and clinical outcome is unclear. In the present study, we retrospectively investigated the occurrence of hypercalcemia (≥10.2 mg/dl after adjustment for serum albumin concentration), leukocytosis (≥14,000/mm^3 with no evidence of infection) or both in lung cancer patients (1149 cases). There were 65 cases (5.7%) of hypercalcemia, 16 cases (1.4%) of leukocytosis and six cases (0.5%) of both hypercalcemia and leukocytosis at the time of first presentation. The occurrence of these two distinct paraneoplastic syndromes in the same patients was more frequent than could have been expected by chance alone ($P < 0.001$). There was a significant correlation between the hypercalcemia–leukocytosis syndrome and performance status ($P = 0.002$). Survivals of patients with hypercalcemia alone (median survival time: MST 3.8 months, $n = 59$), leukocytosis alone (MST 1.9 months, $n = 10$), and the hypercalcemia–leukocytosis syndrome (MST 1.5 months, $n = 6$) were significantly shorter than those without them (MST 9.5 months, $n = 1074$; $P < 0.001$). Moreover, survival of patients with the hypercalcemia–leukocytosis syndrome was significantly shorter than that of patients with hypercalcemia alone ($P = 0.013$). On the other hand, there was no significant difference in survival between the hypercalcemia–leukocytosis syndrome and leukocytosis alone ($P = 0.47$). Multivariate analysis of prognostic factors using the Cox proportional hazards model could not demonstrate that the hypercalcemia–leukocytosis syndrome had independent prognostic significance. In conclusion, our results suggest that the hypercalcemia–leukocytosis syndrome is an additional clinical entity of

*Corresponding author. Present address: Department of Respiratory Medicine and Clinical Research, National Sanyo Hospital, Respiratory Disease Center, 685 Higashi-kiwa, Ube, Yamaguchi 755-0241, Japan. Tel.: +81-836-58-2300; fax: +81-836-58-5219.
E-mail address: a-hiraki@za2.so-net.ne.jp (A. Hiraki).

0169-5002/$ - see front matter
doi:10.1016/j.lungcan.2003.09.006

paraneoplastic syndrome and is an indicator for poorer outcome in lung cancer patients, although the frequency of the combined syndrome is very rare (0.5% of cases over a 10 year interval.

1. Introduction

Paraneoplastic syndromes are systemic and non-metastatic manifestations that cause increased morbidity and possibly mortality in patients with a variety type of cancers [1–5]. Among these paraneoplastic syndromes, hypercalcemia is relatively common in patients with lung cancer [1]. The frequency of hypercalcemia has been reported to range between 10 and 25% (2). Leukocytosis is another common paraneoplastic syndrome, ranging between 16 and 30%, in patients with lung cancer [3–5]. Of note, recent studies have reported that hypercalcemia and leukocytosis simultaneously occur in patients with lung cancer [3–6] and other carcinomas [7–10]. We have described that patients with oral cancers occasionally manifest both hypercalcemia and leukocytosis and that there is a statistically significant correlation between the occurrence of hypercalcemia and leukocytosis [11]. From these observations, we proposed that concomitant occurrence of hypercalcemia and leukocytosis could be categorized as the hypercalcemia–leukocytosis syndrome [11]. However, it is unknown whether the hypercalcemia–leukocytosis syndrome is a specific clinical entity for oral cancers or general one for other malignancies. More importantly, it is also unclear whether cancer patients with both hypercalcemia and leukocytosis exhibit different clinical outcome from patients with hypercalcemia or leukocytosis alone. To determine this, we performed an extensive examination of the clinical records of 1149 lung cancer patients for the occurrence of hypercalcemia, leukocytosis or both in a retrospective manner. Our results show that lung cancer patients manifest the hypercalcemia–leukocytosis syndrome as well and suggest that the hypercalcemia–leukocytosis syndrome is an indicator for poorer outcome in these patients.

2. Patients and methods

2.1. Patients

This study included 1149 consecutive patients with lung cancer who were admitted to the Okayama University Hospital and National Shikoku Cancer Center Hospital between 1986 and 1996. These patients were composed of 871 men and 278 women, with a median age of 66 years (ranges, 20–92). Histologically, there were 442, 324, 55 and 294 patients with adenocarcinoma, squamous cell carcinoma, large cell carcinoma and small-cell carcinoma, respectively. Patients with laboratory or clinical evidence for infection were excluded.

2.2. Diagnostic definition for hypercalcemia and leukocytosis

Hypercalcemia was defined as a serum calcium (Ca) concentration greater than 10.2 mg/dl. When serum albumin concentrations were lower than 4.0 g/dl, Ca values were adjusted according to the formula, adjusted Ca concentration (g/dl) = measured Ca concentration + 4.0 − albumin concentration. Leukocytosis was defined as a white blood cell count exceeding 14,000 μl^{-1}.

2.3. Evaluation of bone metastases

All the patients with lung cancer were examined for bone metastases at the time of their first visit using 99 mTc-MDP. When the presence of bone metastases was suspected, further examination by X-ray, computed tomography (CT) and magnetic resonance imaging (MRI) was conducted to verify bone metastases.

2.4. Statistical analysis

The Chi-square test was used to evaluate correlations between hypercalcemia alone, leukocytosis alone, and simultaneous occurrence of them (hypercalcemia–leukocytosis syndrome). The Chi-square test or trend test was used to evaluate correlations between hypercalcemia–leukocytosis syndrome and several categorical variables. Probabilities of survival were estimated using the Kaplan–Meier method, and differences between patient groups were evaluated by the log-rank test. Prognostic factors were analyzed using the Cox proportional hazard model. All reported P-values are two-sided. A level of $P < 0.05$ was accepted as statistically significant.

Table 1 Patient characteristics

	Total	Hypercalcemia	Leukocytosis	Hypercalcemia–leukocytosis syndrome
No. evaluated	1149	65	16	6
Median age	66	67	58	63
Range	92–20	92–45	75–45	49–75
Sex				
Male	871	59	13	6
Female	278	6	3	0
Performance status				
0	332	4	2	1
1	561	23	2	0
2	122	12	5	1
3	88	17	3	2
4	46	9	4	2
Histology				
NSCLC	835	54	15	6
Adenocarcinoma	442	14	8	2
Squamous cell carcinoma	324	33	5	3
Large cell carcinoma	55	5	1	0
Adenosquamous cell carcinoma	14	2	1	1
SCLC	294	10	1	0
Others	20	1	0	0
Stage				
I	151	4	1	0
II	77	4	0	0
IIIA	178	8	0	0
IIIB	266	22	2	1
IV	477	27	13	5

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

3. Results

3.1. Incidence of hypercalcemia and leukocytosis

Patient characteristics are presented in Table 1. Sixty-five (5.7%) patients developed hypercalcemia and 16 (1.4%) showed leukocytosis at first visit. Among these patients, six cases (0.5%) manifested both hypercalcemia and leukocytosis. Concomitant manifestation of hypercalcemia and leukocytosis was not due to by chance, since there was a statistically significant correlation between the occurrence of hypercalcemia and leukocytosis by chi-square test ($P < 0.001$).

Patients with hypercalcemia–leukocytosis syndrome are listed in Table 2. All of these six patients were male and their median age was 63. Three of them were with squamous cell carcinoma, two with adenocarcinoma, and one with adenosquamous cell carcinoma. Five patients were at clinical stage IV in and one at IIIB. Serum Ca levels in patients with hypercalcemia–leukocytosis syndrome ranged between 10.3 and 14.6 mg/dl (mean, 11.8 mg/dl). The average white blood cell count (WBC) in patients with the syndrome was 24,166 mm^{-3} (range, 14,300–45,500 mm^{-3}). The average WBC in the whole patients involved in this study was 7446.9 mm^{-3} (median, 6800 mm^{-3}).

3.2. Relationship between hypercalcemia–leukocytosis syndrome and clinicopathologic factors

The relationship between hypercalcemia–leukocytosis syndrome and clinicopathologic factors is shown in Table 3. A statistically significant correlation was observed between hypercalcemia–leukocytosis syndrome and performance status (PS) ($P = 0.002$). However, hypercalcemia–leukocytosis syndrome was not correlated with clinical stage ($P = 0.095$), gender ($P = 0.345$), histology ($P = 0.347$), and bone metastasis ($P = 0.104$).

Table 2 Patients with hypercalcemia–leukocytosis syndrome in 1149 lung cancer

Patient no.	Age/sex	Histology	Clinical stage	PS	Invasion of bone	Treatment for lung cancer	Serum Ca (mg/dl)	Leukocyte (mm^3)	CRP (mg/dl)	Survival (months)
1	64/M	AC	IV	3	+	Paliative	10.3	25000	9.3	1.45
2	64/M	SCC	IV	3	+	Paliative	10.6	14300	5.0	1.48
3	59/M	ASCC	IV	2	+	VDS + CDDP	10.7	45500	6.1	1.58
4	75/M	SCC	IV	4	–	CBDCA + ETP	14.6	14700	3.7	0.43
5	49/M	ASCC	IV	4	+	IFO + VDS	12.4	14700	5.8	1.38
6	62/M	SCC	IIIB	0	–	Paliative	12.2	30800	6.0	3.55

AC: adenocarcinoma; SCC: squamous cell carcinoma; ASCC: adenosquamous cell carcinoma; PS: performance status; CRP: C-reactive protein; VDS: vindesine; CDDP: cisplatin; CBDCA: carboplatin; ETP: etoposide; IFO: ifosfomide.

Table 3 Relationship between hypercalcemia–leukocytosis syndrome and clinicopathologic factors

Factor	Hypercalcemia–leukocytosis syndrome	Non-hypercalcemia–leukocytosis syndrome	*P*
Sex			
Male	6	871	0.345
Female	0	278	
Performance status			
0–2	2	1013	0.002
3–4	4	130	
Histology			
NSCLC	6	835	0.347
SCLC	0	314	
Stage			
I–II	0	406	0.096
III–IV	6	737	
Bone metastasis			
Present	3	232	0.104
Absent	3	911	

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer. The Chi-square test or trend test was used to evaluate correlations between hypercalcemia–leukocytosis syndrome and several categorical variables. All reported *P*-values are two-sided. A level of $P < 0.05$ was accepted as statistically significant.

3.3. Relationship between survival and hypercalcemia, leukocytosis or both

Fig. 1 shows survival curves of lung cancer patients with hypercalcemia, leukocytosis or both. Survival in patients with hypercalcemia alone (median survival time: MST 3.8 months, $n = 59$), leukocytosis alone (MST 1.9 months, $n = 10$), and hypercalcemia–leukocytosis syndrome (MST 1.5 months, $n = 6$), was significantly shorter than those in patients without hypercalcemia and leukocytosis (MST 9.5 months, $n = 1074$; $P < 0.001$). Of note, survival in patients with hypercalcemia–leukocytosis syndrome was significantly shorter than that in patients with hypercalcemia alone ($P = 0.013$). On the other hand, there was no significant difference in survival between hypercalcemia–leukocytosis syndrome and leukocytosis alone ($P = 0.47$).

Multivariate analysis of prognostic factors including hypercalcemia–leukocytosis syndrome age, PS, clinical stage, gender, serum Ca concentrations, serum albumin concentrations, serum lactate dehydrogenase concentrations and WBC using the Cox proportional hazards model revealed that hypercalcemia–leukocytosis syndrome had no independent prognostic significance.

4. Discussion

Hypercalcemia and leukocytosis are two of the most common paraneoplastic syndromes that occur in the advanced stages of the illness [3–11]. In the present study, we retrospectively examined 1149 patients with lung cancer for manifestation of hypercalcemia and/or leukocytosis at their first visit. Our results showed that 65 (5.7%) patients manifested hypercalcemia alone, 16 patients (1.4%) leukocytosis alone and six patients (0.5%) both hypercalcemia and leukocytosis. Statistical analysis demonstrates that the concomitant occurrence of hypercalcemia and leukocytosis in these six patients is more frequent than could have been expected by chance alone ($P < 0.001$) and thus suggests that these two paraneoplastic syndromes are closely correlated with each other. These results suggest that the hypercalcemia–leukocytosis syndrome we previously proposed in oral malignancies [11] is also an independent clinical entity in lung cancer.

It has been long recognized that paraneoplastic syndromes such as hypercalcemia and leukocytosis are indicators of poor prognosis in the various types of malignancies [2,5]. Consistent with this, our study confirmed that survival of patients with either hypercalcemia or leukocytosis alone was significantly shorter than that of those without these syndromes. On the other hand, the prognostic value of the hypercalcemia–leukocytosis syndrome has not been determined to date. Our data clearly showed that survival of patients with the hypercalcemia–leukocytosis syndrome was significantly shorter than that of patients with hypercalcemia alone. To our knowledge, this is the first demonstration that suggests that the hypercalcemia–leukocytosis syndrome is an indicator for poorer outcome than hypercalcemia alone in lung cancer patients. However, our results did not prove that the hypercalcemia–leukocytosis syndrome has independent prognostic significance.

Our results also suggest that hypercalcemia and leukocytosis can be caused through a common mechanism. Recent studies have reported that long-term exposure to granulocyte-colony stimulating factor (G-CSF) results in a stimulation of osteoclastic bone resorption in patients with congenital neutropenia [12,13] and in normal rodents [14,15]. Purton et al. described an increase of osteoclast progenitors in G-CSF-mobilized peripheral