Future Surgical Procedures for Peripheral Early Stage Lung Cancer

Tumors with 100% GGO findings on CT images could indicate the suitability of surgical limited resection by VATS. Lesions consisting of between 50% and 100% of GGO in area may also be indication for limited resection in cases less than 2 cm in diameter, and also perhaps in cases consisting of between 10% and 50% GGO finding with a tumor size less than 1 cm in diameter.

The evaluation of limited resection for the small peripheral nodules were reported previously by several researchers,[6,7,9] however different opinions concerning these modalities have been reported.[10,11] There are still controversies concerning limited resection of peripheral small lung cancers. A randomized clinical trial by the Lung Cancer Study Group (LCSG) demonstrated disadvantages of limited resection for T1N0 tumors in relation to lobectomy.[11] Therefore clinical evidence of the usefulness of limited resection for peripheral early stage lung cancers should be proven. The features of peripheral lung cancers suitable for limited resection without lymph node dissection should be clarified. That will make it possible to determine the optimal CT findings for limited resection.

In our experience, even if the primary lesion was less than 1 cm in size, nodal involvement was confirmed histologically in some cases. Prognostic factors may not solely depend on tumor size but also on the percentage of the area of GGO. It is necessary to clarify the findings of CT images of non-invasive cancer by a clinical multicenter study.

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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

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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

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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 ($\leq$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 $\geq$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.

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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*

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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).

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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

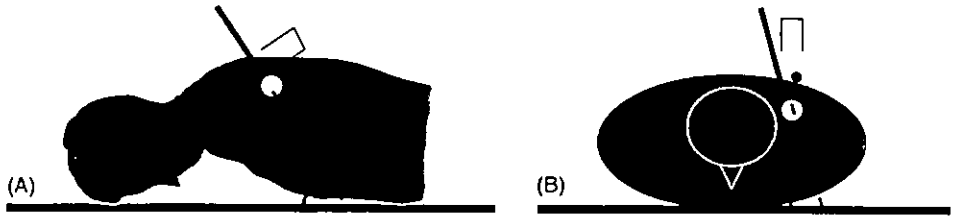

Fig. 1. The schemas of the body position, target lesion and needle direction. The white circle means the target, the black circle means the wire, and the line shows the direction of the needle. Panel A shows the distance from the needle entry point to the lesion and pleura, and the angle from cranio-caudal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

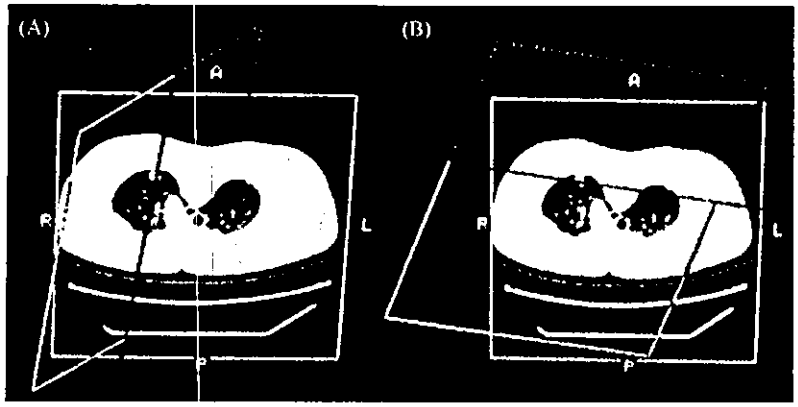

Fig. 2. (A) Induction image of a first oblique image applied as the plane of posterior–anterior axis and cranio-caudal axis. (B) Induction of a second oblique image reconstructed the plane of posterior–anterior and left–right axis.

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].

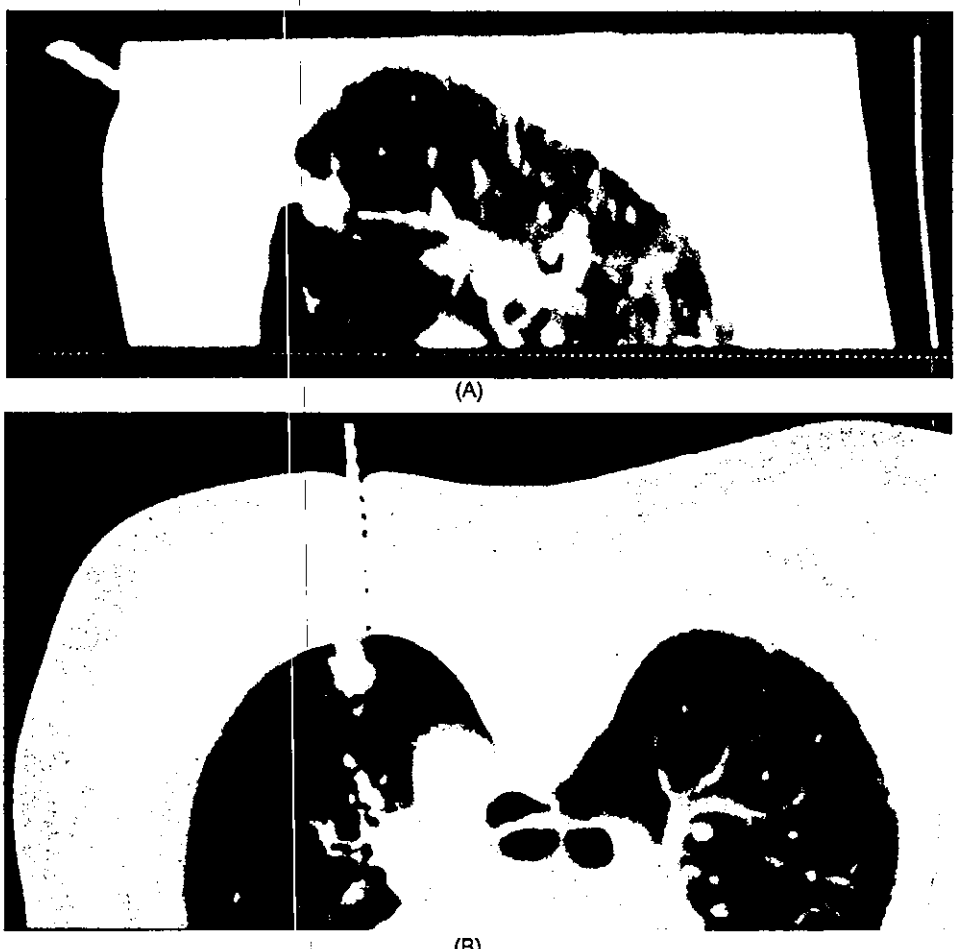

Fig. 3. (A) The first oblique image corresponding to the plane indicated Fig. 2A. (B) The second oblique image corresponding to the plane indicated Fig. 2B.

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.

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Efficacy and Tolerability of Cancer Pain Management with Controlled-release Oxycodone Tablets in Opioid-naïve Cancer Pain Patients, Starting with 5 mg Tablets

Wasaburo Koizumi[1], Hiroshi Toma[2], Ken-ichi Watanabe[3], Kanji Katayama[4], Masaaki Kawahara[5], Kaoru Matsui[6], Hiroya Takiuchi[7], Kunitoshi Yoshino[8], Nobuhito Araki[9], Ken Kodama[10], Hideyuki Kimura[11], Ichiro Kono[12], Hiroyasu Hasegawa[13], Kaoru Hatanaka[14], Kazuaki Hiraga[15] and Fumikazu Takeda[16]

[1]Department of Gastroenterology, School of Medicine, East Hospital, Kitasato University, Sagamihara, Kanagawa, [2]Department of Urology, Kidney Center, Tokyo Women's Medical University, Tokyo, [3]Department of Otolaryngology, Nihon University School of Medicine, Tokyo, [4]First Department of Surgery, School of Medicine, Fukui Medical University, Fukui, [5]Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Sakai, Osaka, [6]Division of Thoracic Malignancy, Osaka Prefectural Habikino Hospital, Habikino, Osaka, [7]Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, [8]Department of Otolaryngology, [9]Department of Orthopedic Surgery and [10]Department of Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [11]Department of Surgery, Okayama Saiseikai General Hospital, Okayama, [12]Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki, Okayama, [13]Second Department of Surgery, Tokuyama Central Hospital, Tokuyama, Yamaguchi, [14]Drug Safety Management Department, Shionogi & Co., Ltd, Osaka, [15]Department of Special Inpatient Division, National Cancer Center Hospital, Tokyo and [16]Comprehensive Regional Medicine, Saitama Medical School, Saitama, Japan

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[1]Department of Gastroenterology, School of Medicine, East Hospital, Kitasato University, Sagamihara, Kanagawa, [2]Department of Urology, Kidney Center, Tokyo Women's Medical University, Tokyo, [3]Department of Otolaryngology, Nihon University School of Medicine, Tokyo, [4]First Department of Surgery, School of Medicine, Fukui Medical University, Fukui, [5]Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Sakai, Osaka, [6]Division of Thoracic Malignancy, Osaka Prefectural Habikino Hospital, Habikino, Osaka, [7]Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, [8]Department of Otolaryngology, [9]Department of Orthopedic Surgery and [10]Department of Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [11]Department of Surgery, Okayama Saiseikai General Hospital, Okayama, [12]Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki, Okayama, [13]Second Department of Surgery, Tokuyama Central Hospital, Tokuyama, Yamaguchi, [14]Drug Safety Management Department, Shionogi & Co., Ltd, Osaka, [15]Department of Special Inpatient Division, National Cancer Center Hospital, Tokyo and [16]Comprehensive Regional Medicine, Saitama Medical School, Saitama, Japan

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Background: We conducted an open-label, dose titration study to assess the efficacy and tolerability of controlled-release oxycodone in the therapy of cancer pain management, starting with a newly developed 5 mg tablet every 12 h.

Methods: Twenty-two Japanese cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks were enrolled. The length of time and the dose needed to attain stable and adequate pain control were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.

Results: Eighteen patients in the efficacy population (18 out of 20, 90%) attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration. The mean length of time was 1.2 days. In these patients, the pain was significantly reduced in intensity, even at 1 h after the initial dose intake. Fifteen patients (68%) reported at least one side effect, but only one patient had to withdraw from the study because of a side effect.

Conclusion: The results suggest that controlled-release oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. This indicates that a lower strength controlled-release oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics.

Key words: oxycodone – 5 mg controlled-release tablets – titration – analgesia – cancer pain

INTRODUCTION

Oxycodone is a semi-synthetic opioid analgesic drug that has been in clinical use for >80 years (1). It effectively relieves both non-cancer and cancer pain in patients (2–4), and has been widely acknowledged as one of the invaluable alternatives to morphine, the parent drug of strong opioid analgesics (5,6).

The strengths of controlled-release (CR) oxycodone tablets legalized in Japan in April 2003 are 5, 10, 20 and 40 mg tablets. Since 1997, however, they have been widely available in the USA and Europe. We anticipated that a starting dose of lower than 10 mg would provide effective analgesia in cancer

For reprints and all correspondence: Wasaburo Koizumi, Department of Internal Medicine, School of Medicine, Kitasato University, 2-1-1 Asamizodai Sagamihara Kanagawa 228-8520, Japan. E-mail: koizumi@med.kitasato-u.ac.jp

patients with moderate pain who had not previously been exposed to opioid analgesics, based on the dose ratio between morphine and oxycodone calculated in previous studies (7–10), which suggested that 5–7.5 mg of CR oxycodone would provide adequate analgesic effects comparable with those of 10 mg CR morphine tablets.

It should also be considered that a lower starting dose may be better tolerated in Japanese cancer patients with moderate pain, because the average body weight of Japanese individuals is much lower than that of Western individuals. Therefore, the starting dose of 10 mg may possibly lead to an overdose for some Japanese patients who have not been exposed to opioid analgesics previously. In addition, a lower starting dose should also be recommended for patients with renal and/or hepatic impairment in comparison with those with normal functions (11). These are the reasons why the 5 mg CR oxycodone tablets were developed to control slight to moderate pain that was not relieved with non-opioid analgesics. The tablet was also expected to be useful for cancer patients for whom a lower starting dose should be considered or a sensitive dose titration should be performed during the opioid treatment.

This was an open-label, 7 day dose titration study in cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks. The aim of this study was to determine the length of time and the dose needed for attaining stable and adequate pain control, and to evaluate the efficacy and safety of CR oxycodone tablets, with a starting dose of 5 mg every 12 h.

SUBJECTS AND METHODS

PATIENTS

This study was conducted over a 3 month period in adult in-patients with cancer pain recruited from 11 centers (13 divisions) in Japan. They were receiving non-opioid analgesics to manage their pain, but with little effect. The patients eligible for the study had to be cooperative, able to take oral medication and able to keep a pain diary. The patients enrolled scored their pain intensity as slight to severe pain on a 4-point categorical (CAT) scale (where 0 = no pain, 1 = slight pain, 2 = moderate pain and 3 = severe pain). They had been treated with non-opioid analgesics until entering the study, e.g. paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), but they had not taken any opioid analgesics over at least the previous 2 weeks. The values of their clinical laboratory tests for liver function (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and total bilirubin) and kidney function (serum creatinine) should not exceed the upper limit of the in-house normal reference range by more than five and six times, respectively. Patients were excluded if they had a history of hypersensitivity to opioid analgesics or if the use of oxycodone or morphine was contraindicated for any reasons. Also excluded were patients who had undergone surgery or palliative radiotherapy for pain over the previous 2 weeks, or who were scheduled to undergo such treatments during the study period.

This study was designed mainly to assess pharmacokinetic profiles of CR oxycodone 5 mg tablet in a single dose as well as to evaluate the safety and efficacy of the CR oxycodone during the titration. For that purpose, 20 cases were considered necessary for the pharmacokinetic analysis and, therefore, we set the target number at 25 cases with the premise that there might be some cases to be excluded from the analysis set. However, infact, we decided to discontinue the study when 22 patients were accumulated, because we judged the number of patients to be sufficient to conduct the pharmacokinetic analysis. The relationship between pharmacokinetics of oxycodone and pain intensity after the first dose will be published separately (in preparation).

All patients gave written informed consent before being enrolled in the study. The institutional review board at each center approved the protocol before the study was initiated. The study was carried out in accordance with the guideline of Good Clinical Practice (GCP) and the ethical principles originating from the Declaration of Helsinki.

TREATMENTS

This was an open-label, dose titration study starting with a 5 mg CR oxycodone tablet given every 12 h. The initial dose was 5 mg and the dose could be titrated against the intensity of pain. If the patient reported their pain intensity as 'moderate' or 'severe' on the CAT scale, the dose could be titrated with the use of 5 and 20 mg CR oxycodone tablets every 24 h. Conversely, the doses could be reduced if the patient experienced intolerable adverse events. Dose titration against the intensity of pain was continued until a stable and adequate pain control with minimal adverse effect was obtained. We considered that adequate pain control was attained when the following conditions were fulfilled: pain-free period lasted at least 48 h; the dose every 12 h was unchanged; no supplemental analgesic dose was taken; the dosing regimen for any non-opioids or adjuvants was unchanged; the patients rated their pain intensity as 'no' or 'slight' on the CAT scale; and any adverse events were tolerable.

Throughout the study, patients were allowed to take immediate release oral morphine preparations as rescue medication whenever breakthrough pain or incident pain occurred. If patients took the rescue medication, an equivalent amount of oxycodone was added to their total daily dose of CR oxycodone tablets. The maximum daily dose of oxycodone (i.e. CR oxycodone tablets plus any rescue dose) permitted in this study was 240 mg.

Patients were not allowed to take any other opioid analgesic during the study. They were allowed to take non-opioid analgesics and adjuvant medications for their specific needs if these drugs had been given before study entry. The dose and route of administration of these drugs had to remain the same throughout the study course as they had been taking until study entry. The use of anti-side effect agents was recommended during the

study. In particular, anti-emetics and laxative agents were commonly used from study entry.

Pain Intensity

Each day, the patients themselves assessed their pain intensity over the previous 24 h. They were also requested to assess their pain intensity at 0 h (i.e. immediately before taking their initial dose of study medication), and at 1, 3, 5, 8 and 12 h after the initial dose intake. At the same points, blood samples were collected concomitantly and assayed for plasma oxycodone and noroxycodoen. They rated their pain intensity on the CAT scale described above, and on a 100 mm visual analogue scale (VAS), where 0 mm = a painless state and 100 mm = worst possible pain. Patients also recorded the number of hours that they were in pain each day and also the number of hours of sleep they had each day.

Evaluation of Pain Control and Length of Time to Attain Stable and Adequate Pain Control

The investigator at each center assessed whether the patient was under stable and adequate pain control in accordance with the criteria described above. The first assessment by the investigator was made 48 h after the initial intake of the study medication. Subsequent assessment was conducted each morning until the patient had attained a stable and adequate pain control.

When the patient attained a stable and adequate pain control within the first 48 h without any dose titration, the time to stable and adequate pain control was recorded as 0 day.

Acceptability of Therapy

Acceptability of therapy was an index based on analgesic effect and side effect of the study medication assessed by patients. Each day, the patients themselves assessed the acceptability of the therapy to them over the previous 24 h and recorded this in a diary. They rated the acceptability of therapy on the 5-point acceptability CAT scale (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). The overall assessment was done in accordance with pain intensity and the occurrence of any adverse events.

Safety Assessments

Safety was evaluated based on the frequency and severity of adverse events, the data for which were obtained by questioning and/or examining the patients and by reviewing the patient's pain diaries and also the results of clinical laboratory tests at study entry and completion of, or withdrawal from, the study. The severity (slight, mild or severe) and seriousness (serious and non-serious) of adverse events was assessed by the investigators.

Statistical Analyses

The percentage of patients who gave a rating of 'good' or 'excellent' for acceptability of therapy were analyzed using the Clopper–Pearson method with a 95% confidence interval (CI).

Changes in the percentage of patients whose pain intensity was 'slight' and 'no' pain were assessed using the McNemar method. Changes in pain intensity (CAT scale and VAS scores) were assessed using the Wilcoxon signed rank test. The following parameters were analysed using the paired *t*-test: number of painful hours per day, number of hours sleep and acceptability of therapy ratings. The percentage of patients attaining stable and adequate pain control and the associated 95% CIs were estimated using the Kaplan–Meier method and Greenwood's method, respectively.

RESULTS

Patient Population

Of the twenty-two cancer patients enrolled in the study, 20 completed the 7 day study period. The efficacy population included 20 patients who were enrolled and did not infringe any of the inclusion or exclusion criteria. Two patients were excluded from the efficacy population because of infringement of the inclusion criteria: one patient had received a fentanyl injection (0.1 mg/day) for pain relief during biopsy 4 days before study entry; and the other patient had not been treated with any analgesic agents before the study. The safety population included all of the 22 patients who were enrolled and had received at least one dose of the study medication.

The mean age and mean body weight of all of the 22 patients were 69.1 years (range 49–80) and 54.5 kg (range 38.0–82.0), respectively. Nineteen patients (86.3%) were male. The most common diagnosis was lung cancer (25.0%), followed by stomach and esophageal cancer. The most common sites of pain were the chest and abdomen.

Two patients withdrew from the study. One withdrew because of the complication of serious pneumonia, which was not considered to be related to the study medication. The other withdrew because of somnolence, which was considered to be related to the study medication. This patient had attained stable and adequate pain control before the withdrawal.

Time Course of Pain Intensity After the Initial Dose

Table 1 shows patients' pain intensity scores (CAT scale) up to 12 h after the initial dose intake of the study medication (one 5 mg tablet). The patients' pain intensity scores decreased significantly by 1 h after the intake and the decreases continued up to 12 h after.

A similar time course of pain intensity was observed when assessed using the VAS. No patient needed supplemental medication until the next dose was given.

Requirements for Titration

Eighteen of the 20 patients (90%) attained stable and adequate pain control during the 7 day study period. Table 2 shows the

Table 1. Changes in pain intensity up to 12 h after the initial dose

Time points (time after initial dose, h)	CAT pain intensity score*		VAS pain intensity score	
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**
0	1.7 ± 0.8	–	44.0 ± 24.8	–
1	1.3 ± 0.9	0.0078	33.0 ± 31.2	0.0022
3	1.2 ± 0.9	0.0078	32.1 ± 31.8	0.0100
5	1.0 ± 0.9	0.0020	27.1 ± 29.9	0.0016
8	1.2 ± 0.9	0.0156	31.8 ± 30.8	0.0314
12	1.3 ± 0.9	0.0469	32.1 ± 30.1	0.0285

$n = 20$ at all time points.
*CAT pain score: 0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain.
**P-value for change from 0 h after the initial dose.

Table 2. Mean length of time to stable, adequate pain control and mean dose needed for stable, adequate pain control*

	Mean ± SD	Minimum	Median	Maximum
Length of time to adequate, stable pain control (days)	1.2 ± 1.9	0	0	5
Dose needed for adequate, stable pain control (mg/day)	16.7 ± 10.8	10.0	10.0	40.0

*Patients attained stable, adequate pain control, $n = 18$.

mean (±SD), minimum, median and maximum length of time and the dose needed to obtain stable and adequate pain control. Mean (±SD) and median length of the time to stable, adequate pain control were 1.2 ± 1.9 and 0 days, respectively. Mean (±SD) and median doses needed for stable and adequate pain control were 16.7 ± 10.8 and 10 mg/day, respectively. The dose ranged from 5 to 20 mg every 12 h. Two patients were unable to attain stable adequate pain control during the study period: one withdrew because of an adverse event (pneumonia), and the other did not want to increase the study medication because of adverse events (sleepiness, itching, sweating and dry mouth). The estimated rate of achievement of stable and adequate pain control at the end of the study was 93.8% (95% CI 82.1–100.0).

Table 3 shows the number and percentage of patients who attained stable and adequate pain control at each dose level. Twelve (68%) of the 18 patients attained it at the dose of 5 mg every 12 h (10 mg/day). All of these patients required no dose titration and attained pain relief that met the criteria for stable and adequate pain control. They attained it within the first 48 h after study entry (length of time to stable and adequate pain control is 0 days).

Change in Pain Intensity During the Study

At study entry, 13 patients (65%) reported their pain intensity to be 'moderate' to 'severe' and seven patients (35%) reported it to be 'slight'. Table 4 shows the patient mean (±SD) CAT scores at study entry reported by the patients, 24 h after their initial dose intake of the study medication, and at the end of the study. The decrease in patients' pain intensity between study entry and 24 h after their first dose of study medication, and that between study entry and at the end of study were both statistically significant. Similar decreases were also observed and found to be statistically significant in making an assessment of patients' pain intensity with the use of the VAS.

Table 3. Number and percentage of patients attaining stable, adequate pain control at each daily dose

Daily dose (mg)	No. (%) of patients attaining stable, adequate pain control
10	12* (68)
20	2 (11)
30	2 (11)
40	2 (11)

*All 12 patients attained stable, adequate pain control on the first day.

The percentage of patients whose pain intensity was 'slight' and 'no' increased during the study. At the study entry, this rate was 35.0% (95% CI 15.4–59.2). The corresponding values at 24 h after the initial dose intake and at the end of the study were 70% (95% CI 45.7–88.1) and 87.5% (95% CI 61.7–98.4), respectively. The increase in the percentage of the patients whose pain was 'slight' and 'no' was statistically significant between study entry and 24 h after their initial dose intake, and between study entry and the end of the study ($P = 0.0082$).

As rescue medication, more than one dose of immediate-release morphine was used in four patients (20%) during the 7 day study period. The mean of the rescue doses per day was 1.3 ± 0.5. Eighty percent of the patients required no rescue medication.

The number of hours each day that the patients were in pain decreased during the study period. At study entry, the median (range) number of painful hours per day was 12.0 h (1.0–24.0). At 24 h after the initial dose intake, it had decreased to 3.5 h (0.1–24.0), and this decrease was statistically significant ($P = 0.0155$). At the end of study, the corresponding value was 1.0 h (0.0–18.0), and this decrease from baseline (at study entry) was also statistically significant ($P = 0.0022$).

There was no change in the number of hours of sleep patients had each night during the study period. At study entry, the mean (SD) number of hours of sleep was 7.4 h (2.1). The corresponding values at 24 h after the first dose intake of the study medication and at the end of study were 7.7 h (2.3) and 7.3 h (1.9), respectively.

Acceptability of Therapy

Figure 1 shows the acceptability of the therapy to patients at study entry and at the end of the study. At study entry, the number of patients who rated the acceptability of the therapy as 'poor' or 'very poor' was 11 (55%); at the end of the study, this decreased to 1 (5%). The change in acceptability of therapy to patients measured on a 5-point acceptability CAT scale

Table 4. Pain intensity at study entry, at 24 h after the first dose and at the end of study

	VAS pain intensity score		CAT pain intensity score		Percentage of 'slight' or 'none' patients (%)	*P*-value**
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**		
At study entry	47.7 ± 26.4	–	1.8 ± 0.7	–	35.0	–
24 h after first dose	28.8 ± 22.3	0.0053	1.2 ± 0.8	0.0098	70.0	0.0588
At the end of the study*	15.7 ± 16.6	0.0025	0.9 ± 0.6	0.0010	87.5	0.0082

$n = 20$ at study entry and 24 h after first dose.
*$n = 16$: at the end of the study (i.e. at 12 h after the final dose), four patients were excluded from the analysis set as "non-evaluated" cases.
**P-value for change from study entry.

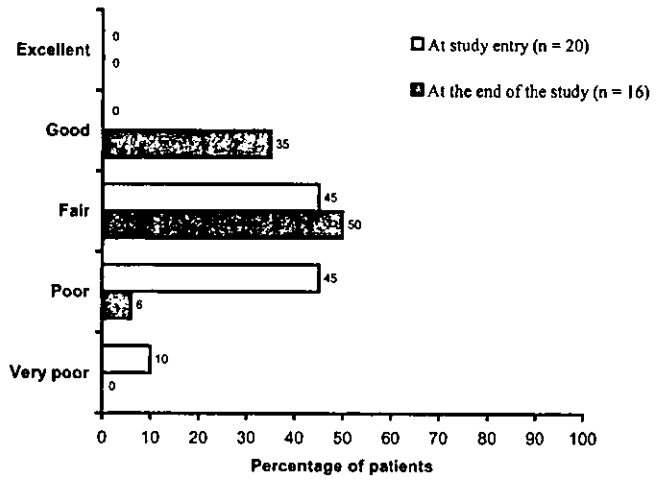

Figure 1. Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

between study entry and at the end of study was statistically significant ($P = 0.0024$).

The percentage of patients whose rating of acceptability on a 5-point acceptability CAT scale was 'good' or 'excellent' was 0% (95% CI 0–16.8) at study entry. However, at the end of study, it increased to 43.8% (95% CI 19.8–0.1).

Safety Evaluations

At least one adverse event, which was considered by investigators to be at least possibly related to study medication (side effect), was observed in 15 of 22 patients (68%; 95% CI 45–86), and 41 cases occurred in total. The common (>10%) side effects were as follows: sleepiness (11 patients, 50%), constipation (seven patients, 32%), nausea (five patients, 28%) and anorexia (four patients, 18%). Most of the reported side effects were slight to moderate in severity. Six cases of severe side effects were reported. Except for one patient who had to discontinue the study due to severe somnolence, all of the patients were able to continue the treatment with the study medication in spite of the side effects. It should be noted that no serious side effects were reported.

Only one patient withdrew from the study because of somnolence that might be related to the study medication. There was no other serious side effect.

Abnormal changes either in white blood cell count or blood creatinine were seen in two patients (9%). Abnormal changes in glutamic oxaloacetic transaminase, glutamaic pyruvic transaminase or positive urinary protein were seen in one patient. Changes in glutamic oxaloacetic transaminase and glutamaic pyruvic transaminase were considered to be clinically significant and considered to be related to the study medication.

Both of the clinical laboratory test values were 21 U before study entry and 51 U at the end of study. The investigator considered that it was impossible to deny the causal relationship between the study medication and the change in laboratory values, although many other drugs were used concomitantly with study medication and, therefore, the exact cause of this abnormal change in laboratory values could not be determined. These changes returned to normal after the medication was stopped.

The value of daily risk was calculated by the method of dividing the total number of incidents of seven common adverse events associated with the opioid, namely constipation, vomiting, nausea, sleepiness, dizziness, dry mouth and pruritus, by the total number of days on which the tablets were taken. The mean value of daily risk in the safety population was 0.19 (29 occurrences in 151 days). The mean value of daily risk in patients who attained stable and adequate pain control was 0.19 (23 occurrences in 125 days).

DISCUSSION

The World Health Organization three-step analgesic ladder has been widely used in cancer pain management (12). In many clinical settings, pharmacological treatment for mild, and sometimes moderate, cancer pain may often be initiated with non-opioid analgesic medication. It may progress to weak and then strong opioid medication in combination with non-opioid treatments as the pain increases in intensity. The only weak opioid analgesics available in Japan are codeine and hydrocodeine. Their analgesic effect is due to their conversion to morphine (13) and they have a ceiling effect. This makes treatment with weak opioid analgesics inappropriate for severe cancer pain management. Hence, the strong opioids are prescribed occasionally when treatment with non-opioid analgesics is ineffective, skipping a trial of weak opioid analgesics in clinical practice. Sometimes, small doses of strong opioids, such as morphine and oxycodone, are used

instead of weaker ones in step 2 for patients who are resistant to or no longer responding to NSAIDs. On the other hand, fixed-dose combination tablets of oxycodone and acetaminophen have been used effectively as weak opioid analgesics to control mainly non-opioid-irresponsive cancer pain in some countries including the USA. We thus conducted an open-label, dose titration study in Japanese cancer patients with pain who had not been taking opioid analgesics, with the starting dose of a 5 mg CR oxycodone tablet every 12 h.

Prior to this study, another study of similar design was conducted in Japanese cancer patients with pain (in preparation). Ninety-two opioid-naïve patients were enrolled in that study and the starting dose was 10 mg every 12 h (twice as high as this study). Twenty-four of 92 patients (26.1%) had to withdraw from the study within 10 days and half of them had to withdraw from the study within 2 days after the study started because of the adverse events (nausea, vomitting, sleepiness, dizziness, etc.) that are commonly associated with opioid analgesics, and most of these withdrawals (21 out of 24) occurred at the starting dose. However, 19 of the 24 patients (79.2%) reported that their pain was less than or equal to 'slight pain' on the pain score (CAT). It should be admitted that the study drug was administered without enough provisions against the side effects. However, a high incidence of sleepiness (five out of 24) and dizziness (three out of 24) associated with the study drug, which ultimately led to discontinuation of the study, suggested that the starting dose of a 10 mg CR oxycodone tablet might be too high for some Japanese cancer patients with pain who had not been taking opioid analgesics. This was possibly because the average weight of Japanese patients is less than that of Western patients.

Furthermore, since oxycodone elimination is delayed by renal (14) or hepatic impairment (15), lower dose CR oxycodone should be considered in determining the starting dose for those patients sensitive to opioids with renal or hepatic impairment. These are the main reasons for development of the 5 mg CR oxycodone tablet in Japan in addition to introduction of 10, 20 and 40 mg CR oxycodone tablets. In the present study, we tried to evaluate the clinical efficacy and safety of CR oxycodone tablets with a starting dose of 5 mg every 12 h in those Japanese cancer patients with non-opioid-irresponsive pain.

Patients who still had a pain unsatisfactorily treated with non-opioid analgesics were enrolled in this study. The aim of this inclusion criterion is to include potential target patients for the 5 mg tablet. Although seven patients (35%) reported baseline pain intensity to be 'slight' at study entry on a 4-point CAT scale, we considered that these patients needed opioid therapy. This was eventually shown by the fact that none of them rated their acceptability of therapy at study entry as 'satisfactory' or 'very satisfactory' on a 5-point acceptability CAT scale. However, at the end of the study, three patients showed satisfaction with the lower dose oxycodone treatment and, moreover, there was no patient who rated their acceptability of therapy as 'poor' or 'very poor'. These results suggest that opioid therapy was indeed needed for the patients with slight pain at study entry in this study.

The 5 mg CR oxycodone tablet (a newly developed formulation) gave significant pain relief 1 h after the first dose, and the subsequent pain scores were kept significantly lower than the pre-dose scores during the following 12 h period. In addition, score for pain intensity was significantly reduced over the 24 h after the first dose intake of 5 mg of study medication as compared with that at study entry. These data indicate that the 5 mg tablet is effective for controlling cancer pain and can be administered quite safely as the starting dose for Japanese cancer patients who have not previously been taking any opioid analgesics.

In this study, 18 (90%) of the 20 patients attained stable and adequate pain control throughout the study period. Two-thirds of them did so on a dose of 5 mg every 12 h without further titration within the initial 48 h (at 0 day). The mean length of time to achieve stable and adequate pain control was 1.2 days. This result was consistent with the findings in two previous studies with CR oxycodone which showed that the mean length of time to stable and adequate pain control was 1.6–2 days (8,16). Although it is common practice to start opioid therapy with an immediate-release formulation and titrate the dose against pain intensity, Salzman and colleagues reported that CR oxycodone was also as readily titrated as an immediate-release formulation (16). Our results support their findings. Moreover, both the patients' rating of their acceptability of therapy on a 5-point acceptability CAT and the overall improvement assessment by the investigator were significantly improved at the end of this study. These results suggest that the use of 5 mg CR oxycodone tablets, if necessary with titration, is acceptable for cancer patients who had not been taking opioid analgesics and is effective for them to achieve stable and adequate pain control in a short period of time.

The 5 mg CR oxycodone tablet was developed to offer a lower starting dose for patients who might experience intolerable adverse events with a starting dose of 10 mg every 12 h. Although a high percentage of patients reported adverse events during this study, most of them were reported to be slight to moderate in severity and only one patient withdrew because of an adverse event (somnolence). Sleepiness, constipation and nausea were the three most common adverse events, all of which are widely known side effects of most opioid analgesics. Another adverse event commonly observed in this study was anorexia, which is commonly reported by cancer patients with pain and can be exacerbated by opioid administration (17).

In conclusion, CR oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. Most of the side effects were tolerable. This indicates that a lower strength CR oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics, including Japanese cancer patients who have a relatively lighter body weight, or patients with renal and/or hepatic impairment.

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