into SN-38 (22,23). Presence of SN-38 in the stool is associated with the occurrence of severe diarrhea as a result of the direct enteric injury caused by SN-38 (24). This phenomenon probably occurs because UGT1A1 is not involved in this step.

Liver metastasis was associated with the development of grade 3–4 diarrhea in both univariate and multivariate analyses in this study. This may be explained by small, but statistically significant differences in the pre-treatment transaminase levels between patients with or without liver metastasis. However, in contradiction to this explanation are that: (1) neither the pre-treatment AST nor ALT level was associated with grade 3–4 diarrhea in this study, and (2) in dose-finding studies of irinotecan monotherapy in patients with liver dysfunction, patients were categorized into subgroups by the PTB and serum AST and ALT levels, criteria of which were three times or five times the upper limit of normal (25,26). Thus, the small difference in the AST and ALT levels in this study is unlikely to be significant from the medical point of view.

The PNC in patients who developed grade 3–4 diarrhea was slightly lower than that in the other patients and the PNC was associated with grade 3–4 diarrhea in the multivariate analysis. Neutrophils play an important role in maintaining the mucosal barrier of the intestine and inflammatory responses against mucosal damage (27). Thus, reduced number, dysfunction, or both, of neutrophils may lead to impairment of the mucosal integrity, rendering these patients prone to develop diarrhea. In addition, the decreased number of neutrophils in the blood is closely related to malnutrition associated with cancer (28), which may in turn be associated with enhanced toxicity during chemotherapy with irinotecan and cisplatin.

In conclusion, the PTB level was significantly associated with severity of neutropenia in patients treated with cisplatin and weekly irinotecan. This will provide a simple and useful marker required for individualized therapy to reduce the risk of harmful chemotherapy.

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Conflict of interest statement

None declared.

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Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

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Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.
Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m^2) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m^2 in level 1, 135 mg/m^2 in level 2 to 150 mg/m^2 in level 3.
Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.
Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4). Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (*cis*-diammine-glycolate-O,O′-platinum II, 254-S) is a second-generation platinum derivative that has an

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antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m^2 and 180 mg/m^2, respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V_{20}) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status (14) 0 or 1; adequate bone marrow function (12.0×10^9/L $\geq$ white blood cell (WBC) count $\geq 4.0 \times 10^9$/L, neutrophil count $\geq 2.0 \times 10^9$/L, hemoglobin $\geq$ 10.0 g/dL and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin $\leq$ 1.5 mg/dL and transaminase $\leq$ twice the upper limit of the normal value), and renal function (serum creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 60 mL/min); and a PaO_2 of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

Treatment Schedule

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m^2 (level 1), 135 mg/m^2 (level 2), and 150 mg/m^2 (level 2). The dose of nedaplatin was 80 mg/m^2 through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensional conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $< 3.0 \times 10^9$/L, neutrophil count $< 1.5 \times 10^9$/L, platelet count $< 100 \times 10^9$/L, serum creatinine level $\geq$1.6 mg/dL, infection $\geq$ grade 2, elevated hepatic transaminase level or total serum bilirubin $\geq$ grade 2, pneumonitis $\geq$ grade 2, peripheral neuropathy, musculoskeletal pain $\geq$ grade 3, fever $\geq$ 38°C, or performance status $\geq$ 2. Chemotherapy was terminated if the toxicities did not

recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever $\geq 38^{\circ}C$, infection $\geq$ grade 2, esophagitis of grade 3, performance status ≥ 3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, Maximum Tolerated Dose (MTD), and Recommended Dose For Phase II Trials

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count $<20 \times 10^9$/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

Study Design, Data Management and Statistical Analyses

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of The Patients

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

Treatment Delivery

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

Toxicity, DLT and MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid

Table 1. Patient characteristics

	n	(%)
Number of patients	18	
Gender		
male	14	(78)
female	4	(22)
Age		
median (range), years	62.5	(46–69)
PS		
0	11	(61)
1	7	(39)
Body weight loss		
< 5%	15	(83)
5–9%	2	(11)
≥ 10%	1	(6)
Clinical stage		
IIIA	10	(56)
IIIB	8	(44)
Histology		
adenocarcinoma	8	(44)
squamous cell carcinoma	6	(33)
non-small cell, not specified	4	(22)

PS, performance status.

replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The V_{20} and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Table 2. Treatment delivery

Dose level	Level 1	Level 2	Level 3
	(*n* = 6)	(*n* = 8)	(*n* = 4)
Number of chemotherapy cycles			
3–4	5	4	2
2	1	3	1
1	0	1	1
Total radiation dose (Gy)			
60	6	7	3
50–59	0	1	0
NE	0	0	1
Radiotherapy delay (days)			
0–4	5	7	2
5–9	1	0	1
NE	0	1	1

NE, not evaluable.

Table 3. Toxicity in all patients

Dose level	Level 1 (*n* = 6)			Level 2 (*n* = 8)			Level 3 (*n* = 4)		
Toxicity grade	2	3	4	2	3	4	2	3	4
Leukopenia	2	3	0	3	3	0	1	2	1
Neutropenia	0	4	1	2	3	1	0	2	2
Anemia	0	0	0	2	0	0	2	0	0
GPT elevation	1	0	0	2	0	0	0	0	0
Total bilirubin elevation	1	0	0	1	0	0	1	0	0
Infection	0	0	0	1	1	0	0	0	0
Allergic reaction	1	0	0	2	0	1	0	0	0
Anorexia	1	0	0	2	0	0	0	0	0
Nausea	0	0	0	1	0	0	0	0	0
Constipation	0	0	0	2	0	0	0	0	0
Esophagitis	1	0	0	2	1	0	0	0	0
Pneumonitis	0	0	1*	1	0	1*	0	0	0
Musculoskeletal pain	1	0	0	1	0	0	1	0	0
Alopecia	4	0	0	4	0	0	0	0	0

GPT, glutamic pyruvic transaminase.
*Pneumonitis was fatal in these patients.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL_{CO}) was not done in this patient. The PaO_2 was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l). The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), % DL_{CO} was 111%, and PaO_2 was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose V_{20} and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.

To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

Objective Response and Survival

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

DISCUSSION

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m^2 and nedaplatin 80 mg/m^2 every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m^2 and cisplatin 80 mg/m^2 were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V_{20} and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subclinical micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.

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Conflict of interest statement

None declared.

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Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

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Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

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70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever ≥ 38°C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles

of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

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Conflict of interest statement

None declared.

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5. CT による肺癌画像診断の進歩

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III　画像検査

5．CT による肺癌画像診断の進歩

Key words：肺癌，X 線 CT，MDCT，肺結節，病期診断/lung cancer, CT (computed tomography), MDCT (multi-detector CT), lung nodule, staging

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要　旨

X 線 CT は，MDCT の登場によって連続した広範囲の薄層 CT を容易にかつ短時間で得られるようになった。これらの薄層多断面の CT 画像に加え，精緻な冠状断像や矢状断像が得られることにより，肺結節の診断，肺癌原発巣の進展範囲診断，リンパ節転移診断ならびに他臓器転移診断にもより高精度かつ効率的に応用されるようになった。

はじめに

肺癌診療において，X 線 CT は必要欠くべからざる画像診断法で，呼吸器科の日常診療のなかで重要な役割を果たしている。今世紀に入って導入され，ここ数年わが国で急速に普及したマルチスライス CT は，より精緻な画像を提供できるようになり，医療現場を変革しつつある。本稿では，このマルチスライス CT を用いた肺癌診断の進歩について概説する。

マルチスライス CT（MDCT）とは

マルチスライス CT（multi-slice CT）は，多検出器型 CT（multi-detector CT：MDCT）とも呼ばれており，MDCT と略されて呼ばれる。従来型のヘリカル CT の検出器は体軸方向に 1 列しか存在しなかったが，マルチスライス CT では 1 本の X 線ビームに対して複数の検出器でデータを取得するものである。そのため一度により多くのデータを得ることが可能である。マルチスライス CT によって，より高速かつ高分解能の画像収集が可能となり，CT の能力は格段に向上した。2000 年頃にマルチスライス CT の実用化が行われ，胸部では全肺野をより薄いスライスで一回の息止めで撮影することが可能になった。マルチスライス CT の登場によって，旧来のヘリカル CT は，シングルヘリカル CT と呼ばれるようになり，マルチスライス CT から区別して呼ばれるようになった。マルチスライスの列数も 4 列，16 列，64 列と増加し，わが国でも急速に多列化が普及しており，本年に入って 320 列という機種も商業的に供給されるようになった。

マルチスライス CT の特徴

マルチスライス CT が従来のヘリカル CT と最も異なる点は，検出器が多数の検出器に細かく分割されていることである。一回の検査でさまざまなスライス厚の画像が再構成できることが特徴の一つであり，シングルヘリカル CT にはなかった利点である。マルチスライス CT は，それぞれの検出器がらせん状に回転しながら撮像し，画像再構成の段階で該当スライスに最も近い複数の点から画像再構成がなされる。このような方法によって，16 列のマルチスライス CT であれば従来のシングルヘリカル CT に比べて，おおむね 16 倍のデータ量が得られることになる。マルチスライス CT の利点は多数あるが，特に肺癌の診断の領域では，以下の三点が重要な点である。

1．薄いスライス厚の画像を高速撮像

このことによりシングルヘリカル CT と比べて体軸方向の空間分解能が向上し，検出器の列数が多いほどより向上することになる。たとえば，16 列の場合は 10 秒程度の呼吸停止下に，1 mm スライスの画像が全肺野（肺尖から肺底部まで）で撮像可能となる。これは，より画質の良好な MPR 像（multi planner reconstruction）や，3 次元表示などにも応用可能である。またスライス厚の設定

Progression of CT Diagnosis for Lung Cancer

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をやや厚くすると，一回の呼吸停止下に頸部から骨盤部まで撮像することも可能で，肺癌の場合には原発巣の状態やリンパ節転移の診断に加え，遠隔転移診断も一度に行える利点がある。

2．再構成可能な横断像のスライス厚の選択肢が広い

このことは一回の撮像でスライス厚の違う画像が得られることを意味する。例えば，全肺を細かいデータで一度採取しておき，肺癌などの主病巣の結節の病変部や問題となるリンパ節のみを 1 mm 程度の薄いスライスで再構成し，それ以外の病変がないと思われる部分は 5 mm 程度のやや厚いスライスで画像を再構成することが可能である。1 mm 程度の薄いスライスで全肺野を再構成してモニタで読影するのが理想的ではあるが，CT 検査を行った全患者にすべて 1 mm 再構成を行うと保管データ量が膨大になるという欠点がある。

3．X 線被曝量の低減

X 線データをより細かく効率的に使い，またスキャンのスピードが速くなることで X 線被曝量の低減が可能である。前述のごとくシングルヘリカル CT とは異なり，薄層 CT を撮影するために二度目のスキャンが不要なことも被曝量の低減に寄与する。また，多くの多列検出器 CT に搭載されている，相対的に空気の多い肺を撮影する際に自動的に X 線照射線量を低減できるシステムの応用により，胸部 CT の患者被曝線量のさらなる低減が可能となった。

マルチスライス CT の特徴を生かした肺癌診断

1．小結節診断のアプローチ

CT では単純 X 線に比べて肺の小結節がたくさん見つかる。特に MDCT では，従来のシングルヘリカル CT と比べてより薄層で，より画質のよい CT 画像が容易に得られるようになったので，数多くの小結節が見つかる。これらの小結節に対しては，その小病変部を 1 mm 程度の連続的な thin-section CT を再構成してアプローチするとより詳細な読影が可能になる。①境界明瞭な結節で，すりガラス陰影を有しない場合と，②結節全体がすりガラス陰影を示す場合，③辺縁部がすりガラス陰影を示す場合に大きくわけて考えると，マネージメントに役立つ[1]。辺縁部がすりガラス陰影を示し内部に充実部を持つタイプは，周辺部に肺胞上皮進展部を伴う腺癌である可能性が高く[2]，その充実部にエアブロンコグラムが捉えられることが多い。

2．小結節のマネージメント

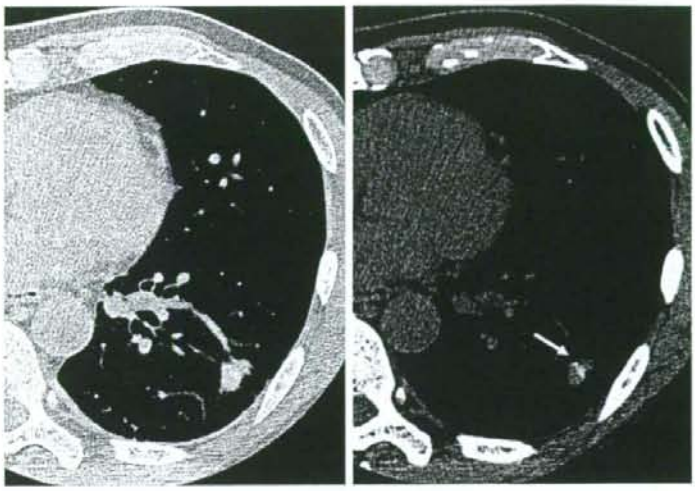
小結節の thin-section CT を再構成する際に，肺野条件だけでなく縦隔条件も同時に再構成して比較すると，肺野条件ではわかりにくかった結節内の小石灰化が描出され，肉芽腫の診断に有用なことがある（図 1）。さらに造影 CT を行って，小結節内の造影程度により質的診断に導く方法もある。ただ長径が 1 cm に満たないような小結節は，画像診断はもちろん，開胸生検以外での診断も困難である。

したがって，CT で偶然に見つかるような小結節に対するマネージメントとして，胸部放射線専門医の集まりである Fleischner Society が 2005 年にガイドラインを出した[3]。この数年間の胸部 CT 検診で見つかる小結節に関する報告を再検討しガイドラインとしてまとめたもので，8 mm 以下の小結節に対しては，基本的にはまず経過観察をすることが勧められている。その方法は小結節の大きさに加え，喫煙者などの高リスク群と非喫煙者などの低リスク群に分けて経過観察の期間を設定していることが特徴である。ただ 8 mm 以上の結節に対しては，PET や造影 CT，生検が勧められるとしているが，これに関する詳細なガイドラインは出ていないのが現状である。

境界明瞭な小結節は，肺転移の場合は原発巣の情報があれば診断は比較的容易であり，現実に増大する小結節で最終的に悪性であると診断されるものは，既知の悪性腫瘍がある場合が多いことが理由の一つである[4]。偶然見つかる境界明瞭な小結節としては，肺内リンパ節がある。肺内リンパ節は，中下葉の胸膜直下か 1 cm 以内に存在する，長径 12 mm 以下の境界明瞭な小結節という特徴を有するので，診断が比較的容易である[5]。

3．原発巣の広がり診断

MDCT で MPR 像を作成することによって，肺癌の原発巣の進展範囲診断に，これまでの CT に付加した画像情報を与えてくれることがある。MPR 像は冠状断像や矢状断像など任意の断面で



a|b

図 1　小石灰化を有する肺結節

高分解能 CT で，左下葉に辺縁不整な結節を認め，周囲血管の集中像も見られる（a）。薄層 CT の縦隔条件で，結節内の小石灰化が淡く描出されている（→）（b）。肉芽腫と診断して，念のため経過観察を行っている。

の画像再構成が可能であることより，肺癌の複雑な進展や既存の臓器や器官との関連がより把握しやすくなる場合がある。特に冠状断像では，腫瘍の気管や気管支との連続性，縦隔側への進展，大血管との関連などが理解しやすい。また腫瘍と葉間胸膜面との関係の評価には矢状断像が優れている[6]（図 2）。

胸膜播種は T4 に分類されており，胸膜播種の診断がつくと手術適応はない。胸膜播種の CT 所見は胸壁に接する小結節，葉間胸膜面の小結節とされ[7]，多数のある程度の大きさの小結節が CT で確認できる場合は診断が容易であるが，一つの小結節のみがみられる場合を胸膜播種と診断すると偽陽性が増えることになり，実際は診断に苦慮することが多い。胸膜播種巣は通常小さいため 1 cm スライスの CT 像では診断が困難な場合が多いが，MDCT では，薄いスライス厚の CT を連続して広範囲で撮像できるため，胸膜播種の診断には適しているといえよう。特に冠状断や矢状断の MPR 像で胸膜播種の診断が明瞭になる場合がある（図 3）。

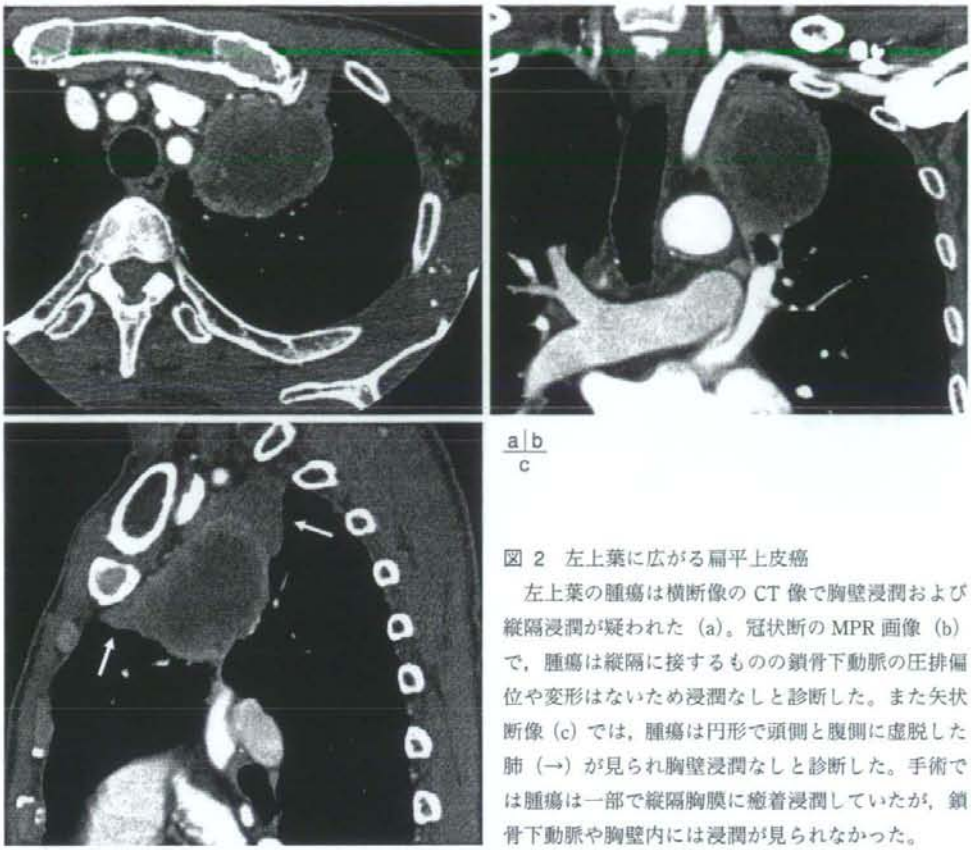
4．肺門，縦隔リンパ節転移の診断

縦隔リンパ節の CT 診断に関する報告はこれまで数多くあり，MDCT 時代になっても大きさによる診断を基準とする点では大きな変化はない。肺門リンパ節の画像診断の報告には必ずしも満足すべきものがなかった。肺門部は血管と気管支が複雑に絡み合い，その間隙にリンパ節が存在するため，造影 CT で 1〜2 mm 程度の薄層に再構成して観察すると肺血管との分離がよくなり，肺門リンパ節が観察可能になる。MDCT では造影剤血中濃度が高く，短い時間内に全胸部を薄層で撮影できるために，肺門部の薄層造影 CT をルーチン検査で得ることができる。

病変のある肺葉の肺門側気管支周囲にあるリンパ節が短径 1 cm に満たなくても腫大して認識できる場合は，転移陽性のことが多い。肺門リンパ節を血管から分離すること，また比較的小さな肺門リンパ節の形状を評価するのに，MDCT での薄層造影 CT が有用である（図 4）。

5．腹部臓器転移の診断

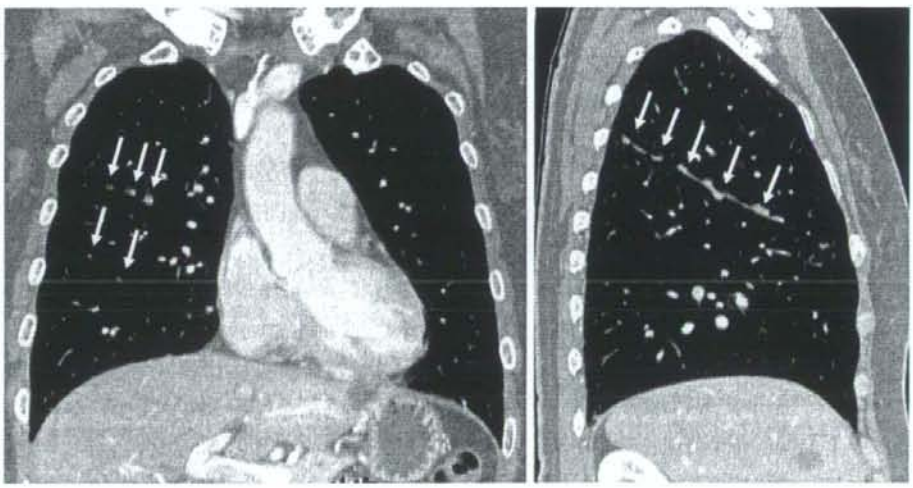
腹部臓器の転移診断にも CT は重要である。MDCT の登場によってこれらの診断能そのものには大きな向上は見込めないが，MDCT では一度の造影剤注入で胸部 CT を撮影するのと同時に腹部から骨盤までの CT をも撮影できる。したがっ



a|b
c

図 2　左上葉に広がる扁平上皮癌

左上葉の腫瘍は横断像の CT 像で胸壁浸潤および縦隔浸潤が疑われた（a）。冠状断の MPR 画像（b）で，腫瘍は縦隔に接するものの鎖骨下動脈の圧排偏位や変形はないため浸潤なしと診断した。また矢状断像（c）では，腫瘍は円形で頭側と腹側に虚脱した肺（→）が見られ胸壁浸潤なしと診断した。手術では腫瘍は一部で縦隔胸膜に癒着浸潤していたが，鎖骨下動脈や胸壁内には浸潤が見られなかった。



a|b

図 3　肺癌の胸膜播種（右下葉原発の腺癌）

冠状断（a）および矢状断（b）の MPR 画像で，葉間胸膜上に小結節が多発しており（→），胸膜播種と容易に診断できる。

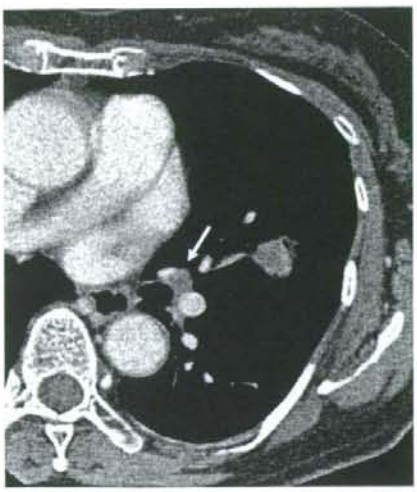


図 4　左肺門リンパ節転移（左上葉原発の腺癌）
薄層の造影 CT で，左葉間の肺門リンパ節（11 番）が肺動脈と明瞭に識別でき，腫大していることがわかる（→）。手術で転移が確認された。

て治療前の初回の胸部 CT 検査の際に，同時に腹部全域の CT 検査を一回の造影剤使用で撮影，評価可能である。医療効率を上げ，患者により負担の少ない検査でより多くの診療情報を提供できるという利点がある。

おわりに

X 線 CT では，マルチスライス CT の登場によって連続した広範囲の薄層 CT を容易に得られるようになったことで，肺結節の診断，肺癌原発巣の進展範囲診断，リンパ節転移診断や他臓器転移診断にもより高精度かつ効率的に応用されるようになった。

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III　画像検査

6. びまん性肺疾患の CT 診断の進歩

Key words：びまん性肺疾患，慢性閉塞性肺疾患，特発性間質性肺炎，多列検出器 CT（MDCT），3 次元高分解能データ解析/diffuse parenchymal lung disease, chronic obstructive pulmonary disease (COPD), idiopathic interstitial pneumonia (IIP), multidetector CT (MDCT), volumetric data analysis

藤本公則*,**

要　旨

びまん性肺疾患の CT 診断は，最近の CT 技術の進歩により，高分解能 CT を用いた肺小葉レベルの所見解析のような微細形態診断に加え，MDCT による高速撮像や volumetric data 取得が可能となって，呼吸運動を利用した動態解析や多方向断面による微細構造の観察や測定，CT 値を利用した定量評価などが新たに行われるようになってきた。今後は疾患別に種々の解析法を駆使していくことになるが，これらの情報をどのように臨床の現場に還元していくかが重要である。

はじめに

概して，びまん性肺疾患は胸部単純 X 線写真でびまん性陰影を呈する疾患の総称であり，多種多様な疾患，病因を包括する。

びまん性肺疾患における CT 診断の進歩としては，CT 技術の進歩と疾患に対する CT 所見解析の進歩に大きく分けられる。CT 技術の進歩として，高分解能 CT，螺旋スキャンの開発と多列検出器 CT（multidetector CT：MDCT）によって大量の連続データ取得が可能になったこと，コンピュータの発達により高精細で種々の解析が可能になったことなどが挙げられ，特に慢性閉塞性肺疾患（chronic obstructive pulmonary disease：COPD）における CT データを用いた各種解析法の重要性が挙げられる[1]。疾患に対する CT 所見解析の進歩としては，高分解能 CT における末梢肺野構造の解剖学的な理解，特に Miller の 2 次小葉を基本とした所見解析法[2)3)]が広く理解されるに至り，膨大な検討結果とエビデンスが蓄積され，特に特発性間質性肺炎（idiopathic interstitial pneumonias：IIPs）の診断における臨床-画像-病理（clinical-radiological-pathological：C-R-P）診断の重要性が認識され，その診断基準，鑑別診断に CT 所見が組み込まれた[4]ことが挙げられる。

本稿では，びまん性肺疾患のうち慢性閉塞性肺疾患と特発性間質性肺炎における CT 診断について，前述の CT の進歩という点を中心に概説し，その研究の一部を紹介する。

慢性閉塞性肺疾患の CT 診断

1. COPD の気腫病変の評価

気腫病変の CT による評価法としては，気腫腔と判定する低吸収域（low attenuation area：LAA）の CT 値（Hounsfield unit：HU）の閾値を設定して強調し，肺野全体に占める LAA の範囲を評価する方法（density mask program）[5]が一般的で，主に上・中・下肺野の代表とする CT 横断画像における LAA の占める程度を視覚的にグレーディング（ランク分け）する半定量的方法は，気道の閉塞性障害を示す呼吸機能検査と相関性が高い[6]ことが知られている。その後，気腫腔と判定する LAA の CT 値の閾値を決定し，その領域をコンピュータ解析で呼び出して面積を計算し，肺野全体の面積で除し，LAA%として評価する方法[7]のほうが定量性，客観性，再現性に優れ，コンピュータ自動解析も行いうる客観的定量評価法として報告された。最近ではより精度の高い方法を目指して，volumetric data を用い立体的に評価することも一般的となりつつある（図 1）。自動解析によっ

Multidetector CT Diagnosis for Diffuse Parenchymal Lung Diseases：Up to Date

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