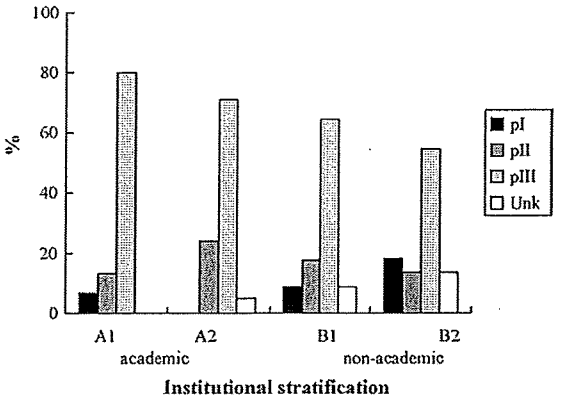

Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

Table 3 Pathological stage in patients with complete surgery according to the stratified institution

Pathological stage	Institutional stratification				Total
	A1	A2	B1	B2	
I–II	2	4	8	4	18
III	5	6	18	8	37
Total	7	10	26	12	55

and N-classifications were pT1 in 22 patients, pT2 in 35, pT3 in 23, and pT4 in 18, and pN0 in 15 patients, pN1 in 19, pN2 in 56, and pN3 in 4. Pathological stage was stage I in 9 patients, II in 17, IIIA in 45, and IIIB in 20, respectively. The proportion of pathological stage III patients tended to be higher in large academic institutions (Fig. 1, $p = 0.13$). Breakdown of pathological stage in 55 patients who underwent complete surgery according to the stratified institution group was shown in Table 3. As for the proportion of pathological stage III patients, no significant difference was observed between institutions.

3.3. Radiotherapy parameters (Table 4)

A CT-simulator was used for planning for 26 patients. Ninety-one patients were treated with opposed AP-PA fields, and field reduction during the course of radiotherapy was done for 48%. Three-dimensional treatment was used in only 2 patients. Photon energies of less than 6 MV were used for 34 patients (34%). Dose prescription by isodose line technique was performed for only 8 patients (8%). The median field size was 9 cm × 11 cm, and the median total dose was 50 Gy. The planning target volume included the ipsilateral hilus in 80%, ipsilateral mediastinum in 86%, contralateral mediastinum in 68%, contralateral hilus in 9%, ipsilateral supraclavicular region in 30%, and contralateral supraclavicular region in 22%. Institutional stratification was found to influence several radiotherapy parameters. A photon energy of 6 MV or higher was used for 73% of patients in A1, 77% in A2, and 80% in B1 institutions, whereas it was used for only 23% of patients in B2 institutions (Fig. 2, $p < 0.0001$). A Cobalt-60 unit was used only in 5 B2 institutions. The planning target volume included the contralateral mediastinum for more than 70% of patients in A1 to B1 institutions, whereas it was included in only 46% of patients treated in B2 institutions ($p = 0.011$).

Table 4 Radiotherapy parameters

Simulation method	
CT-simulator	26
X-ray simulator	38
X-ray simulator + CT	26
Missing	7
Treatment technique	
AP-PA	91
Oblique	2
Three-field	1
Three-dimensional conformal	2
Other	2
Missing	1
Photon energy	
60 Co	5
<6 MV	29
≥6 MV	64
Missing	1
Dose prescription	
Isodose line	8
Point	91
Total dose	
≤3000 cGy	1
3001–4000 cGy	6
4001–5000 cGy	49
5001–6000 cGy	37
6001–7000 cGy	6
Missing	1
Median total dose (cGy)	5000
All fields treated each day (%)	83
Median field size (cm)	
Left-right	9 (range, 5–23)
Cranio-caudal	11 (range, 5–20)
Field reduction during radiotherapy (%)	48
Field included (%)	
Ipsilateral hilus	80
Ipsilateral mediastinum	86
Contralateral mediastinum	68
Contralateral hilus	9
Ipsilateral supraclavicula	30
Contralateral supraclavicula	22

3.4. Use of chemotherapy

Thirty patients (31%) received systemic chemotherapy. For 21 patients, chemotherapy and PORT were administered concurrently, mainly using a platinum-based, two-drug combination. For 9 of the 30 patients, platinum-based chemotherapy was used as induction therapy. Oral fluorouracil was used for 9 patients.

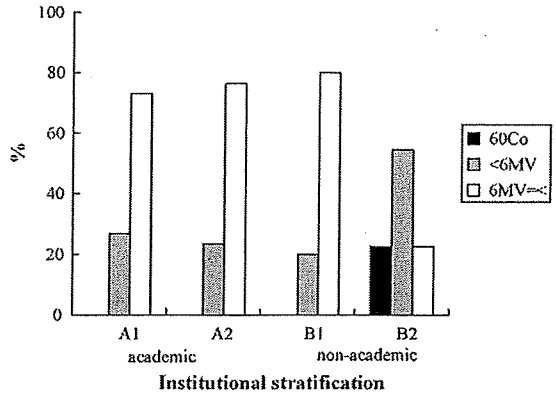

Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

3.5. Failure pattern and preliminary clinical outcome

The site of first failure was local in 6, regional in 5, and distant in 31. Of the patients who developed failure, the median time to first failure was 7 months. Although the current PCS has limitations in terms of outcome analysis due to a short follow-up period and significant variations in follow-up information according to institutional stratification [10,12], overall survival for the entire group was 88% at 1 year and 63% at 3 years, with a median follow-up period after PORT of 1.7 years.

4. Discussion

The results of the present PCS reflect national practices for PORT for NSCLC in Japan. However, when interpreting our data, it is important to note that they were limited to patients who received radiation therapy. We have no information about patients who did not receive radiation therapy after surgery. Thus, we have no data concerning the percentage of patients who underwent radiation therapy after surgery. Analysis of the national practice process for all patients with NSCLC in the adjuvant setting is beyond the scope of this study.

All eligible patients in this study received radiation therapy after publication of the PORT meta-analysis that emphasized deleterious effects in patients receiving PORT, especially for patients with completely resected N0-1 disease [4]. Since then, the clinical focus on adjuvant treatment has largely shifted to chemotherapy, which has become part of the postoperative standard of care for patients with NSCLC [5,6,8]. In the United States, use of PORT has substantially declined due to the lack of proven survival benefit [13]. However, PORT was still incorporated as an option in recent clinical trials that recruited patients with pathological N2 disease [5,7]. The recent analysis of Surveillance, Epidemiology, and End Results (SEER) data in the United States demonstrated that PORT was associated with improved survival for patients with N2 disease [14,15]. In addition, a recent clinical study has reported promising results for combined PORT and chemotherapy using modern radiotherapy techniques [7,8]. Thus, the current clinical question is whether adjuvant chemotherapy combined with PORT improves survival for patients at high risk for locoregional failure compared with adjuvant chemotherapy alone. Taking all of the evidence together, we conclude that PORT still plays an important role in the adjuvant setting. We believe that this PCS study provides basic data of current practice regarding PORT in Japan.

Results of the present study demonstrated that patients who received PORT accounted for 16% of all patients with NSCLC who received radiation therapy in Japan between 1999 and 2001. Of all 99 patients, 65 had pathological stage III disease (45, stage IIIA; 20, stage IIIB). Using a median field size of 9 cm × 11 cm, a median total dose of 50 Gy was delivered mainly through opposed AP-PA fields. Three-dimensional conformal treatment was infrequently used. Field size reduction during the course of radiotherapy was done for almost half of the patients. A dedicated CT-simulator was used for 26 patients. The PORT meta-analysis was criticized because the authors included several old studies in which a cobalt machine was used for radiotherapy. It was pointed out that suboptimal administration of PORT using outdated techniques counterbalanced the beneficial locoregional effects of PORT treatment in the meta-analysis [16]. Because of potential pulmonary/cardiac toxic effects of mediastinal radiotherapy, PORT should be delivered with modern radiotherapy techniques using CT-based three-dimensional conformal treatment planning, a technique with which target volumes and normal tissue constraints are precisely defined. Although the patients included in this PCS survey were treated between 1999 and 2001, the modern radiotherapy era, 34% of all patients were treated using photon energies <6 MV, including five patients who were treated using a cobalt machine. Institutional stratification influenced several radiotherapy parameters in PORT for NSCLC. As shown in the previous report for small-cell lung cancer in Japan [17], smaller non-academic institutions (B2) provided a lower quality of care for their patients. Planning target volume typically included the ipsilateral hilus, ipsilateral mediastinum, and contralateral mediastinum in A1 to B1 institutions, whereas the contralateral mediastinum was included for only 46% of patients treated in B2 institutions. Although there is controversy concerning prophylactic nodal irradiation in the setting of definitive radiation therapy, PORT for patients with pN2 NSCLC should include the contralateral mediastinum. Proportion of patients with pathological stage I–II who underwent complete surgery did not differ between stratified institution groups. Thus, it was considered that omission of treating the contralateral mediastinum in B2 institutions was not caused by unbalance in stage distribution. We speculate that this discrepancy in care was due mainly to the extremely small number of radiation oncologists in B2 institutions. We also found that obsolete equipment such as Cobalt-60 units were still used, especially in non-academic institutions treating only a small number of patients per year. The proportion of patients treated with 6 MV or higher photon energies was significantly higher in A1 to B1 institutions than in B2 institutions. A Cobalt-60 unit was used only in B2 institutions. The present study again confirms differences in the practice of radiotherapy according to institutional stratification status.

We consider that the structure of radiation oncology is a domestic problem specific to each country. The results represent intrinsic problems with the structure of radiation therapy in Japan. Considering the current immaturity of the Japanese structure of radiation oncology, PCS still perform an important role in monitoring structure and process, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers.

5. Conclusions

Through the audit survey and subsequent data analyses, the PCS established nationwide basic information on the practice of PORT for NSCLC in Japan. Even after the publication of the PORT meta-analysis, PORT was used for a considerable proportion of patients receiving radiotherapy. However, this PCS documented that outdated modalities such as cobalt-60 units were still used in small non-academic institutions during the study time frame. Thus, the current PCS confirmed the continuing existence of variation in the practice of radiotherapy according to institution stratification.

Conflict of interest

We have no conflict of interest in connection with this paper.

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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 $\geq 38°C$ 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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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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HEPATOLOGY

Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: Retrospective study

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Key words
abdominal lymph nodes, external beam radiotherapy, hepatocellular carcinoma, metastasis.

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Abstract

Aim: This study was conducted to evaluate the effect of external radiation therapy on lymph node metastases from hepatocellular carcinoma (HCC).

Methods: A total 28 patients with cytopathologically proven HCC were subjected to radiation therapy over a 5-year period, and treatment was continued in all cases. All patients underwent irradiation with a total dose ranging between 46 and 60 Gy in daily 2.0-Gy fractions, five times a week.

Results: Among the metastatic lesions treated, 18 (64%) and five (18%) patients achieved partial responses and complete responses, respectively. The 1- and 2-year overall survival rates and the median survival time were 53% and 33%, respectively, and 13 months in patients given external beam radiation therapy (EBRT) for a non-palliative, near-cure intent ($n = 21$).

Conclusions: Although lymph node metastasis from HCC is sensitive to EBRT, the intent of EBRT should be limited to palliation. For palliative purposes, it is useful in treatment with 50 Gy in 25 fractions for these patients.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Japan, with a mortality of 28.6 per 100 000 in 2001. During recent years, because of the progress achieved in treatment methods, the likelihood of improving local control and the survival rate in HCC has increased. However, prolongation of life might also result in the increased development of metastatic lesions. Liver, lung, bone, lymph node, adrenal, brain and elsewhere are known as the metastatic regions of HCC. Above all, lymph node metastasis (LNM) is likely to accompany systematic metastases, and a treatment method has not yet been established. As external beam radiation therapy (EBRT) has long been used in cancer therapy, we felt that it might be of benefit in the treatment of metastatic HCC lesions.

In our institution EBRT has been used in HCC patients with LNM since 1994. Because the role and efficacy of EBRT for LNM from HCC has not been determined, a retrospective study was conducted of our experience over the past 5 years to evaluate the objective response of LN lesions from HCC and side-effects of EBRT. This study constitutes a preliminary report on the results for 28 HCC patients with LNM who received EBRT.

Method

EBRT was performed on 28 HCC patients diagnosed with LNM until July 2005 (Table 1). All 28 patients had HCC confirmed by hepatoma resection or liver biopsy. Patients with cholangiocarcinoma or mixed HCC and cholangiocarcinoma were excluded from this study. EBRT was not the initial treatment in all patients (Table 2). After resection, transcatheter arterial embolization (TAE), radiofrequency ablation (RFA), or percutaneous ethanol injection therapy (PEIT) of the primary tumor, the regular follow-up consisted of monthly liver function tests plus serum alpha-fetoprotein (AFP). Also, enhanced computed tomography (CT) scans were performed every 6 months on all patients. Diagnosis of LNM was made by the enhanced CT scans during the clinical follow-up studies (Table 3).

The lymph nodes were not the only site of recurrences in all patients. Characteristics of intrahepatic tumors at the time of positive LNs are shown in Table 2. Information regarding other metastasis at the same time is listed in Table 3.

In this paper, the locoregional abdominal lymph node metastasis from HCC was grossly classified to hepatic portal, peripancreatic and para-aortic nodes on the basis of the increase

Table 1 Patient characteristics

Characteristic	Number	Rate (%)
Age (years)		
Range	50–81	
Median	66.5	
Sex		
Male	24	86
Female	4	14
Ascites		
Slight	1	3.5
Immediate	1	3.5
None	26	93
Bilirubin (mg/dL)		
<2	27	96
2–3	0	0
>3	1	4
Serum albumin (g/dL)		
>3.5	13	46.5
2.8–3.5	14	50
<2.8	1	3.5
PT (serum)		
>80%	8	29
60–80%	16	57
<60%	4	14
γ-GTP (IU/L)		
≤75	19	68
75–150	6	21
≥150	3	11
AFP status (μg/L)		
≤20	11	39
20–400	11	39
≥400	6	22
Child-Pugh classification		
A	16	57
B	12	43

AFP, α-fetoprotein; PT, prothrombin time; γ-GTP, gamma glutamine transpeptidase.

follows the natural flow of lymph. Portal lymph nodes include the hepatoduodenal ligament and common hepatic artery lymph nodes. Peri-pancreatic nodes consist of posterior pancreaticoduodenal and anterior pancreaticoduodenal lymph nodes. Paraaortic nodes are composed of celiac trunk and superior mesenteric artery as well as the middle colic artery lymph nodes.

Patient characteristics are listed in Table 1. The Karnofsky performance status score was greater than 90% in almost all patients. The median period from initial therapy for the primary tumors to EBRT for LNM was 34.6 months (3.2 months to 6.1 years). Whether or not patients received EBRT was a matter of physician preference because of the extent of the tumor, or at the discretion of the attending surgeon, and, ultimately, depended on the consent of the patient.

The Child-Pugh classification score was based on the levels of serum bilirubin, serum albumin, prothrombin time prolongation, presence or absence of ascites, and encephalopathy (Table 1).

Table 2 Characteristics of intrahepatic tumor

Characteristic	Number	Rate (%)
Intrahepatic tumor number		
Multiple (≥2 nodules)	8	67
Solitary	4	33
Maximal diameter (cm)		
≤2 cm	6	50
>2 cm	6	50
Vascular invasion		
(+)	1	8
(–)	11	92
TNM staging by LCSGJ		
I	2	17
II	3	25
III	6	50
IV	1	8
Previous therapy for intrahepatic tumors		
Resection	8	29
TAE	19	68
RFA	15	54
PEIT	5	18

LCSGJ, Liver Cancer Study Group of Japan; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; TAE, transcatheter arterial embolization.

Treatment plan

Patients received limited-field EBRT using a linear accelerator with 6-MV photon. The design and delivery of EBRT used a CT scan of the disease during the simulation process. The radiation portals encompassed the involved nodes with generous margins (2 cm) and were usually less than 100 cm^2. Parallel-opposed portals were frequently used. An isocentric technique was used and the source to axial distance (SAD) was 100 cm. The median tumor dose was 50 Gy (range 46–60 Gy) in daily 2.0-Gy fractions, five times a week. Twenty-two patients (79%) were given 50 Gy in 25 fractions. The total dose was less than or equal to 60 Gy in all patients. Two patients with ascites received the same dose (Table 4).

Follow-up

Enhanced CT scans between pre- and post-EBRT were compared. A complete response (CR) was defined as complete disappearance of all clinical and radiographic evidence of disease. A partial response (PR) required a 50% or greater reduction in the sum of the products of the longest diameter and its perpendicular of measurable lesions. Progressive disease was defined as an increase of ≥25% in the sum of the products of the longest diameter and its perpendicular, as compared with the lowest value recorded. Objective response (OR) was calculated for CR and PR.

For AFP positive patients, the serum AFP was also assayed in the first follow-up. AFP changes were compared with two investigations about 3 months apart, from pre-EBRT to 1 and half months after completion of EBRT. AFP decline required a value under 20 μg/L or a difference of 10% from a previous assay. Toxicity was evaluated according the Radiation Therapy Oncology Group criteria (version 2.0).[1]

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Table 3 Characteristics of the target lymph node (LN) lesion

Characteristic	Number	Rate (%)
Location of the lesions (cumulative)		
Portal LN	10	36
PALN	12	43
Pre-pancreatic LN	2	7
Supra-clavicular LN	4	14
Peri-gastric LN	2	7
Peri-esophageal LN	2	7
Mediastinal LN	2	7
Axillary LN	1	3.6
Subphrenic LN	1	3.6
Hilar LN	1	3.6
Maximal diameter of LN		
≤2 cm	4	14
2–5 cm	19	68
≥5 cm	5	18
LN number		
Multiple	10	36
Solitary	18	64
Group		
Locoregional	17	61
Distant	11	39
Aim of RT		
Near-cure	21	75
Palliative	7	25
Other metastasis at the time of positive LN		
None	23	82
Lung	2	7
Bone	1	3.6
Systemic LN	1	3.6
Bone and lung and IVC	1	3.6

IVC, inferior vena cava; PALN, para-aortic lymph node; RT, radiotherapy.

Table 4 Radiotherapy method

	Number	Rate (%)
Total dose (Gy)		
46Gy/23Fr	1	4
50Gy/25Fr	23	82
60Gy/30fr	4	14
Treatment period (days)		
Range	21–63	
Median	35	
RT technique		
Three-dimensional conformal	8	28
Four-field box	15	54
AP-PA opposed fields	4	14
Wedge pair	1	4
Field length of *y*-axis direction (mm)		
<100	14	50
≥100	14	50
Field length of *x*-axis direction (mm)		
<100	20	71
≥100	8	29

AP, anteroposterior; Fr, fractionations; PA, posteroanterior.

Statistical methods

Statistical analyses were performed using StatView Dataset File version 5.0 J for Windows computers (North Carolina, USA). Overall survival (OS) was calculated from the first date of RT. Survival time was plotted using the Kaplan-Meier method. The Cox regression model was used to detect associations between survival and the following valuables: gender, serum AFP and γ-glutamyltransferase levels, intrahepatic tumor status (tumor size and number), LN status (location, number and size), and Child-Pugh classification.

Results

Follow-up

At the end of follow-up, 16 patients (57%) had died. Median follow-up time was 5.2 months (range 2–42 months).

Response and survival

In all patients, 18 (64%) and five (18%) patients achieved PR and CR, respectively (Table 5). In patients given EBRT for the near-cure intent (not palliative intent), the 1- and 2-year overall survival rates were 53% and 33%, respectively, and the median survival time (MST) was 13 months (Fig. 1).

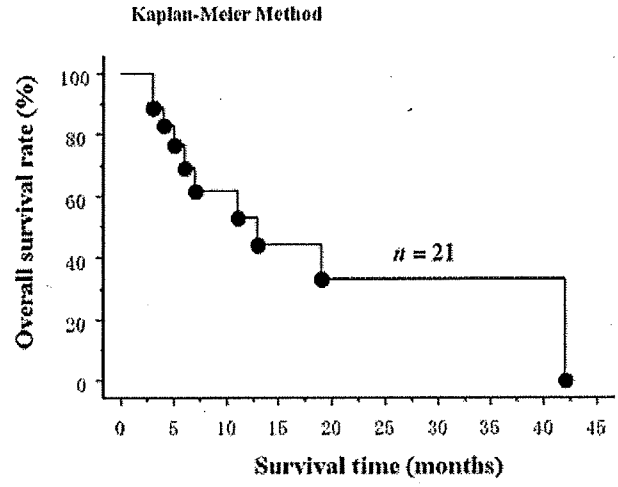

Figure 1 Overall survival curves for lymph node metastasis from HCC according to metastatic lesions.

Of the 28 HCC patients, 12 patients (43%) showed a significant decrease in their AFP levels, including three patients who returned to a normal level (≤20 μg/L). There were eight patients who showed AFP level increases or remained at the pretreatment level after EBRT.

Prognostic factors

The results of univariate and multivariate analyses of survival are listed in Table 6. Two factors appeared to be independently

Table 5 Univariate and multivariate analyses ($n = 21$) in relation to survival in patients given external beam radiation therapy (EBRT) for near-cure intent

Independent variable	Patients	Kaplan-Meier survival				Univariate analysis		Multivariate analysis	
	(*n*)	1-year (%)	2-year (%)	Median (M)	*P*-value	RR	*P*-value	RR	*P*-value
γ-GTP (IU/L)									
≤50	10	60.0	40.0	13.0	0.973	1	0.973	1	0.153
>50	11	48.0	32.0	11.0		1.02		34.28	
Sex									
Female	4	66.7	66.7	—	0.485	1	0.497	1	0.359
Male	17	51.4	27.4	13.0		2.04		0.029	
AFP (μg/L)									
≤30	8	57.1	38.1	19.0	0.705	1	0.707	1	0.417
>30	13	43.6	21.8	11.0		1.30		0.365	
Previous therapy for intrahepatic tumors									
Resection	6	30.0	0	6.0	0.047	1	0.065	1	0.060
Without resection	15	61.7	46.3	19.0		0.26		0.061	
Group									
Distant	6	80.0	40.0	19.0	0.401	1	0.411	1	0.384
Locoregional	15	40.3	26.9	11.0		1.96		0.15	
Child-Pugh classification									
A	12	30.5	30.5	7.0	0.352	1	0.363	1	0.057
B	9	87.5	32.8	19.0		0.52		0.014	
Maximal diameter of LN (cm)									
≤3.5	12	59.3	59.3	—	0.251	1	0.266	1	0.585
>3.5	9	46.7	15.6	11.0		2.21		2.74	
LN number									
Multiple	7	44.4	22.2	7.0	0.379	1	0.389	1	0.211
Solitary	14	55.9	37.2	19.0		0.56		0.058	
Response to EBRT									
OR	17	55.1	41.3	13.0	0.857	1	0.858	1	0.246
NC	4	50.0	25.0	11.0		1.14		0.11	

AFP, α-fetoprotein; LN, lymph node; M, months; NC, no change; OR, objective response; RR, relative risk.

Table 6 Side-effects of external beam radiotherapy

	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal				
Anorexia	11	1	0	0
Diarrhea	1	0	0	0
Gastro/duodenal ulcer	2	8	0	0
Dermatitis	3	2	0	0
Hepatic				
ALT (GPT)	6	7	0	0
Bilirubin	3	0	0	0
Bone marrow				
White blood cells	8	10	0	0
Platelets	12	5	4	0

ALT (GPT), alanine aminotransferase (glutamate pyruvate transaminase).

associated with the risk of death: (i) the Child-Pugh classification, with a worse prognosis with decreasing classification; and (ii) previous resection for intrahepatic tumors, with a worse prognosis.

Side-effects from external beam radiation therapy

No side-effects equal to or more than grade 3 such as loss of appetite and nausea, gastrointestinal bleeding or perforation induced by EBRT were seen. However, regarding bone marrow, thrombocytopenia of grade 3 was seen in four patients (14%) (Table 6).

Discussion

The predominant majority of HCC cases are restricted to the liver. Regional LNM are uncommon in HCC patients. The incidence of LN involvement in patients with HCC is between 1.6% and 5.9% during treatment,[2,3] but the incidence in autopsy cases has been as high as 30%.[4,5] During recent years an increasing incidence has been noted, possibly due to the interventional procedures carried out for patients with HCC, such as surgical resection, TAE, as well as PEIT.

Patients with LNM from HCC have a dire prognosis, even if radical resection is performed by experienced surgeons.[6–8] The survival in these patients treated with resection varied markedly

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and ranged from 2 to 87 months (usually 3 months or less).[6–8] LN involvement is generally not the limiting factor in determining symptoms or survival, both of which relate more to hepatic parenchymal involvement or distant metastatic disease. The LN involvement is not rare and is documented by cited autopsy series. Therefore, in those series of unresectable cases LN status has generally been neglected. Also, TAE and PEIT were not suitable for these patients. EBRT was tried in these patients but was limited to only four HCC patients with abdominal LN involvement. These were described in two reports and one phase I clinical trial from China, appearing at an interval of 10 years. The former two papers showed CR in all, with improved longer survival. In the later paper, all of the 29 HCC patients with LN involvement who received EBRT achieved objective responses and their symptoms were completely relieved.[9] In our results, 64% and 18% of patients achieved PR and CR, respectively. In another study, Zeng *et al.* reported the radiosensitivity of HCC LN and concluded that LNM from HCC is sensitive to EBRT (50 Gy in 25 fractions).[10] Sixty-two patients with regional LNs received local limited EBRT (40–60 Gy in daily 2.0-Gy fractions). After EBRT, PR and CR were observed in 37% and 60% of patients, respectively, and the MST was 9.4 months.

The incidence of LNM in HCC patients is much higher in the autopsy series than in the clinical data.[2–5] This might mean LN involvement usually does not result in death of HCC patients. In our study, there was no significant difference in overall survival between one group with locoregional LNM and the other group with distant LNM ($P = 0.401$). This might suggest that RT for the locoregional LNM from HCC could not lead to improvement in survival.

As to the irradiation dose in our series, almost all patients were treated with 50 Gy (82%). Zeng *et al.*[9,10] recommended that the suitable irradiation dose should be limited to less than 56 Gy, because gastrointestinal bleeding incidence was much higher (33.3%) in patients given 56 Gy or higher. Additionally, they concluded that EBRT with 25 fractions of 2 Gy was an effective palliative treatment for patients with LNM from HCC presenting with good performance status.[10] Radiation complications consistently increased as the radiation dose increased, and gastrointestinal bleeding was a serious complication.[10] In our study, no gastrointestinal side-effect was observed. Our recommendation for a suitable radiation dose is 50 Gy.

In this study, AFP could not be used as a predictor in HCC patients with LNM treated with EBRT. This could be explained as lack of intrahepatic tumor and/or distant metastasis control, which resulted in treatment failure. Although LNM from HCC is sensitive to EBRT, the intent of EBRT should be limited to palliation. EBRT is useful in treatment with 50 Gy in 25 fractions for these patients.

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A Rod Matrix Compensator for Small-Field Intensity Modulated Radiation Therapy: A Preliminary Phantom Study

Keiichi Nakagawa, Kiyoshi Yoda*, Yoshitaka Masutani, Katsutake Sasaki, and Kuni Ohtomo

Abstract—**A compensator made of a tungsten-based rod matrix has been proposed for small-field intensity modulated radiation therapy. The compensator was attached to a 6 MV linac gantry head. The proposed compensator could modulate the X-ray intensity with a step of 10% and a minimum transmission of 2.5%.**

Index Terms—**Compensator, IMRT, intensity modulation, radiotherapy.**

I. Introduction

The concept of inverse planning and intensity modulated radiation therapy (IMRT) was proposed by Brahme [1]. The inverse planning is a mathematical optimization procedure in order to deliver sufficiently high dose to a tumor while minimizing dose in healthy organs located adjacent to the tumor. Using the resulting inverse planning solution, the IMRT can be physically realized by two different ways: a dynamic way and a static way.

The dynamic technique utilizes motor-driven multileaf collimators (MLCs) comprising narrow metal bars (leaves) aligned parallel to each other. The irradiated X-ray intensity can be spatially modulated by moving MLCs during X-ray beam delivery. This MLC-based IMRT has been widely accepted because intensity modulation can be automatically planned by using a treatment planning computer. An additional advantage that has been recently reported is a tracking capability for a moving target [2], [3]. A disadvantage of the MLC-based IMRT is that it requires much longer delivery time thereby increasing the chance of organ movements during treatment.

Meanwhile, compensators for high energy X-ray treatment were proposed long time ago [4], and Brahme suggested this as a means for intensity modulation [1]. Several research groups have employed this compensator-based IMRT [5]–[10]. Although the static compensator simplifies the treatment delivery with reduced beam-on time, technologists need to enter the treatment room and exchange compensators port by port. Other disadvantages of compensator-based IMRT are the fabrication time as well as constantly produced compensator wastes.

Recently, dosimetrically less precise compensators for quick fabrication have been proposed [11]–[13], where the compensator can be automatically exchanged. However, these fabrication methods required complicated machines. We have developed a rod matrix compensator that does not require an expensive fabrication machine. The proposed compensator can be manually fabricated within 10 min, and it can be reused without producing wastes.

II. Methods and Materials

Fig. 1(a) shows a photograph of 11 different compensator rods each comprising tungsten compound for X-ray intensity attenuation and wood support for keeping the total rod length to 50 mm. The cross section has a dimension of 5 mm × 5 mm. The tungsten compound has a density of 19.3 g/cm^3 (Heavy Metal, Sumitomo Electric) while the wood support has a density of 0.35 g/cm^3. The tungsten compound and the wood support were bonded by adhesive resin, and each rod has a specific identification (ID) number printed on a surface.

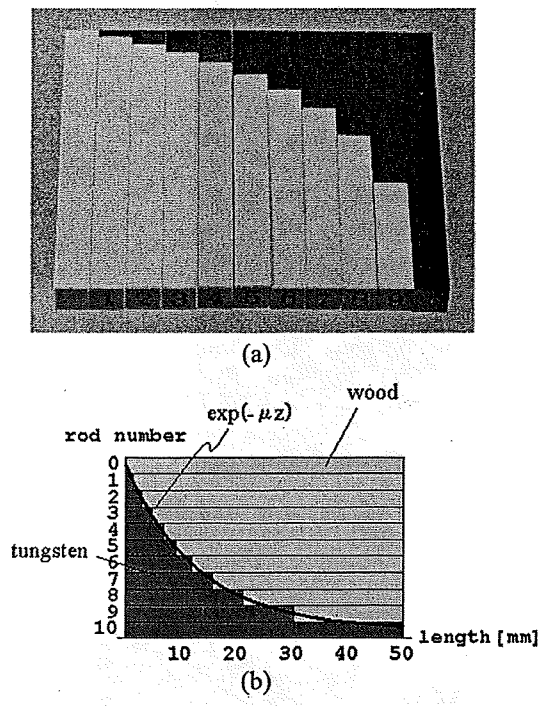

Fig. 1. (a) A photograph of the compensator rods each comprising tungsten compound for intensity modulation and wood support for keeping the total rod length to 50 mm. (b) The length of the tungsten compound was optimized to provide a constant incremental step of 10% attenuation.

Fig. 1(b) shows a mathematical diagram that describes how to determine the length of the tungsten compound for providing a constant incremental step of 10% X-ray attenuation. Each tungsten length is determined by an exponential function $exp(-\mu z)$ where μ is a linear attenuation coefficient of the tungsten compound for a given X-ray energy and z is the length of the tungsten compound. The attenuation caused by the wood support is ignored.

Fig. 2 shows a photograph of the compensator fabrication unit including a metal wall having a foldable portion, a rod matrix piled up inside the wall, a base stand, and a 5 mm thick acrylic base plate that interfaces between the metal wall and the base plate. To support the rod matrix at the bottom, a transparent acrylic plate (1 mm thickness) was inserted, in parallel to the acrylic base plate, into the groove provided near the bottom of the metal wall. Each rod was manually piled up to make an 11 by 11 rod matrix. The foldable part of the metal wall remained open during the piling up process. Because each rod has an ID number corresponding to a particular attenuation level, it was straightforward to pile up the rods according to a given intensity map. After piling up 11 by 11 rods, another 1 mm thick transparent acrylic cover plate was inserted into another groove provided near the top of the metal wall. Finally, the open portion of the metal wall was folded and locked firmly to immobilize the rod matrix.

Fig. 3 depicts a photograph of the resulting compensator attached to the gantry head of a 6 MV Mitsubishi C-arm linac, CRS-6000. For preliminary testing purpose, the distance between the X-ray source and

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