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ORIGINAL ARTICLE

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Results of a preliminary study using hypofractionated involved-field radiation therapy and concurrent carboplatin/paclitaxel in the treatment of locally advanced non-small-cell lung cancer

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Abstract

Background. We aimed to evaluate the feasibility and efficacy of hypofractionated involved-field radiation therapy (IFRT) omitting elective nodal irradiation (ENI) with concurrent chemotherapy for locally advanced non-small-cell lung cancer (NSCLC).

Methods. Between July 2004 and July 2006, ten patients with locally advanced NSCLC were included in this study. One had stage IIIA and 9 had stage IIIB disease. The treatment consisted of IFRT in fractions of 2.5 Gy and weekly carboplatin (CBDCA)/paclitaxel (PTX). Hypofractionated IFRT with a median total dose of 65 Gy with median percent total lung volume exceeding 20 Gy (V20) of 20.2%, and a median of five courses of chemotherapy with weekly CBDCA (area under the curve, 1.5–2.0)/PTX (30–35 mg/m^2) were given to all patients.

Results. The median survival time and the 1-, 2-, and 3-year overall survival rates were 29.5 months and 90.0%, 58.3%, and 43.8%, respectively. No elective nodal failure was encountered during the median follow up of 18.2 months. No acute or late toxicities of grade 3 or worse were observed. No in-field recurrence occurred in the group with a total dose of 67.5 Gy or more, but there was such recurrence in 83.3% of those in the group with less than 67.5 Gy.

Conclusion. Hypofractionated IFRT with weekly CBDCA/PTX was a feasible treatment regimen. Hypofractionated IFRT with a total dose of 67.5 Gy or more could be a promising modality to improve the treatment results in patients with locally advanced NSCLC.

Key words Involved-field radiation therapy (IFRT) · Elective nodal irradiation (ENI) · Three-dimensional conformal radiation therapy (3DCRT) · Non-small-cell lung cancer (NSCLC) · Carboplatin (CBDCA) · Paclitaxel (PTX)

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Introduction

At present, the standard evidence-based treatment for advanced non-small-cell lung cancer (NSCLC), based on data in patients with locally advanced disease, is considered to be concurrent chemotherapy (CHT)-radiation therapy (RT) with a platinum-based regimen.[1] This concurrent CHT-RT provides a median survival time (MST) of 16–17 months, a 1-year overall survival (OAS) rate of 60%–70%, and a 2-year OAS rate of 30%–40%,[2–5] but these results should be open to further improvement. In addition, there is a problem regarding the fact that grade 3/4 radiation esophagitis occurs in 20%–30% of these patients.[3–5]

Local recurrence is one reason for the poor survival rate after RT, and it has been reported that an improvement in local control leads to increased survival in locally advanced NSCLC.[6,7] Therefore, intensification of the in-field effect to improve local control has previously been attempted. However, even though an increase in the total dose and a shortening of the overall treatment time are effective for

improving the local control, problems remain due to the increase in severe esophagitis and pneumonitis.

Recently, involved-field radiation therapy (IFRT) omitting elective nodal irradiation (ENI) to achieve improved local control by high total dose irradiation, without increasing toxicity, has been attempted for locally advanced NSCLC, and the results of these attempts suggested that it might be possible to irradiate safely with a high total dose using IFRT.[8,9] After the publication of these results, we introduced IFRT for locally advanced NSCLC within affiliated institutions of Hiroshima University, in 2001. In addition, we started a preliminary study in 2004 to evaluate the feasibility and efficacy of hypofractionated IFRT with concurrent carboplatin CBDCA)/paclitaxel (PTX). The once-daily fraction is 2.5 Gy, in order to improve the in-field control due to the high total dose irradiation with a higher fraction dose and to also to shorten the overall treatment time.

Patients and methods

Between July 2004 and July 2006, a total of ten patients with locally advanced NSCLC were enrolled in this preliminary study and were evaluated. Before inclusion, all patients signed a written study-specific informed consent. In addition to giving them the details of this study, we also explained that the treatment would be cancelled if they rejected the designed treatment of this study during the treatment period. Eligibility criteria included patients with locally advanced stage IIIA-N2 disease or stage IIIB disease (excluding malignant pleural effusion, malignant pericardial effusion, and lymphangitic carcinomatosis), histologically or cytologically confirmed NSCLC, age between 20 and 74 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no prior therapy for this malignancy, and adequate laboratory and pulmonary functions. Adequate laboratory function included a leukocyte count of 4000/mm^3 or more, platelet count of 100 000/mm^3 or more, hemoglobin 9.5 g/dl or more, total bilirubin level less than or equal to the upper limit of normal, and creatinine clearance of 60 ml/min or more. Adequate pulmonary function was defined as a forced expiratory volume in 1 s of more than 1.0 l and PaO_2 of 70 torr or more. Any patients with previous malignancies or severe complications (such as obvious interstitial pneumonitis, advanced pulmonary emphysema, and poorly controlled diabetes) were excluded. Before therapy, all patients were evaluated clinically with a history, physical examination, laboratory examination, radiographic studies, pulmonary function test, and electrocardiogram (ECG). The laboratory examination included a complete blood cell count, liver function studies, renal function studies, and measurement of electrolytes. The radiographic studies included chest X-ray, thoracic-abdominal computed tomography (CT), head magnetic resonance imaging (MRI), and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan was not routinely performed.

The patient and tumor characteristics are shown in Table 1. The patients' median age was 68 years (range, 54–74 years); nine were males, and one was female. Five (50.0%) presented with squamous cell carcinoma, four (40.0%) with adenocarcinoma, and one (10.0%) with large-cell carcinoma. One (10.0%) had stage IIIA disease (T2N2; $n = 1$) and nine (90.0%) had stage IIIB (T1N3, $n = 1$; T2N3, $n = 5$; T4N0, $n = 1$; T4N1, $n = 1$; T4N2, $n = 1$). Regarding the staging, all patients underwent thoracic-abdominal CT, head MRI, and bone scintigraphy. Whole-body FDG-PET/CT was performed in four patients (40.0%).

All patients were treated with three-dimensional conformal radiation therapy (3DCRT) that was planned with a three-dimensional radiation treatment planning system. All patients underwent treatment-planning CT of the chest for identification of the target and normal anatomy. The treatment-planning CT was performed with continuous slices measuring 5 mm in thickness and with a long scan time of 3 s or more per image without breath-holding, throughout the whole lung and tumor. Only lymph nodes with a short-axis diameter of 10 mm or more on CT were included in the gross tumor volume (GTV-LN) without histological confirmation, in addition to the primary tumor (GTV-P). However, when lymph node involvement was suspected on FDG-PET/CT according to diagnosis by a PET specialist, lymph nodes with a short axis of less than 10 mm were included in the GTV-LN. In addition, the clinical target volume (CTV) was defined as the GTV-P plus the GTV-LN. The planning target volume (PTV) was con-

Table 1. Characteristics of patients and tumors

Patient no.	Age (years)	Sex	PS	Histology	T	N	M	Stage	Location of primary tumor
1	57	M	0	SQ	2	3	0	IIIB	Rt. LL
2	60	M	0	AD	1	3	0	IIIB	Rt. UL
3	65	F	0	AD	2	3	0	IIIB	Lt. UL
4	74	M	0	SQ	2	3	0	IIIB	Lt. UL
5	72	M	0	SQ	4	2	0	IIIB	Rt. LL
6	70	M	0	SQ	2	2	0	IIIA	Lt. LL
7	73	M	0	SQ	4	0	0	IIIB	Lt. UL
8	72	M	1	LC	2	3	0	IIIB	Rt. UL
9	58	M	1	AD	4	1	0	IIIB	Lt. UL
10	54	M	0	AD	2	3	0	IIIB	Rt. UL

PS, performance status; SQ, squamous cell carcinoma; AD, adenocarcinoma; LC, large cell carcinoma; Rt., right; Lt., left; LL, lower lobe; UL, upper lobe

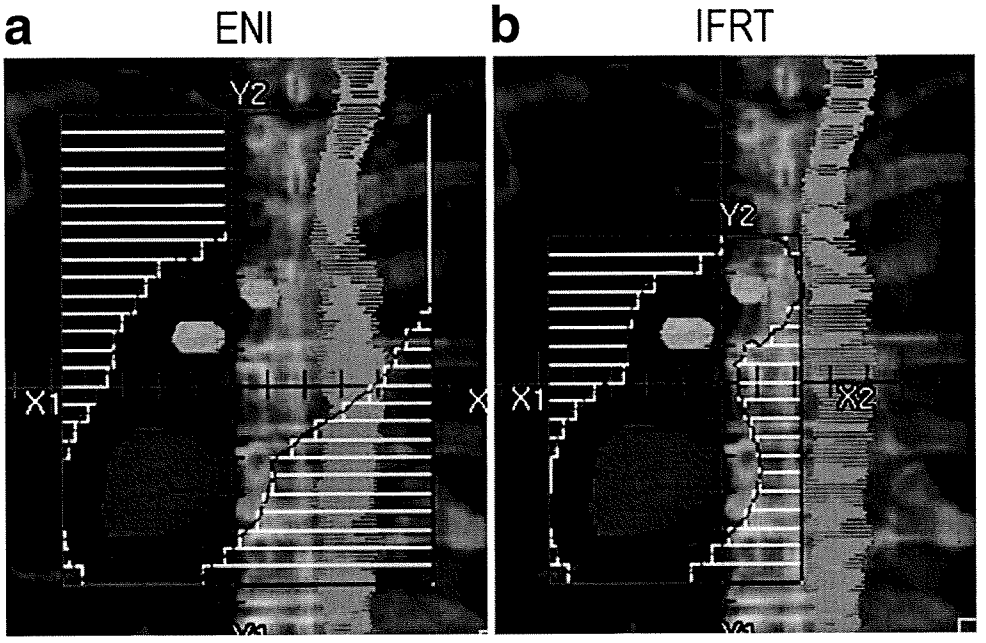

Fig. 1a,b. Digitally reconstructed radiographs (DRRs) demonstrating **a** the typical elective nodal irradiation (ENI) field and **b** the involved-field radiation therapy (IFRT) for a patient with stage IIIA non-small-cell lung cancer (NSCLC). The primary tumor is displayed in *red*; metastatic lymph nodes are displayed in *green*; the esophagus is displayed in *orange*. On DRR of IFRT, the esophagus is outside the radiation field

toured around the CTV with a three-dimensional margin of 10–15 mm (thus making allowances for the location of the primary tumor, the respiratory mobility of the tumor, and the setup margin). In addition, a port margin of 5 mm was set around the PTV. The difference between the ENI and IFRT fields is shown in Fig. 1. The doses were calculated at the isocenter with heterogeneity correction algorithms, using both a superposition method (6 patients) and a convolution method (4 patients). The hypofractionated IFRT was delivered on a linear accelerator, using a 6- to 10-MV photon beam. The hypofractionated IFRT was delivered via a coplanar technique or a noncoplanar technique with multiple fields to deliver a dose of 2.5 Gy once daily in five fractions weekly, and all radiation fields were treated every day. In the course of IFRT, field reductions according to the tumor volume reduction were permitted.

The fraction dose setting in this study was selected based on the preliminary results reported by Kimura et al.,[10] which included accelerated hyperfractionated IFRT (66–75 Gy in 1.5-Gy twice-daily fractions) +/– concurrent CHT. Before the induction of IFRT, irradiation by using accelerated hyperfractionation was considered for IFRT to shorten the overall treatment time. However, we thought that twice-daily fractions might not be practical under clinical conditions, and we decided to use once-daily fractions of 2.5 Gy, whose biologically effective doses (BED) Gy 10 and BED Gy 3 in a day were almost equivalent to that of twice-daily fractions of 1.5 Gy. It was prescribed that the dose variation within the PTV be limited to between 90% and 107% of the prescribed dose. The maximum dose to the spinal cord was kept at less than 40 Gy. The percent total lung volume (the volumes of both lungs minus the CTV) exceeding 20 Gy (V20) was kept to less than 30% in principle, as a higher volume was a predictive factor for the risk of radiation pneumonitis.[11,12] The limitation of the V20 value was considered based on the findings of the Radiation Therapy Oncology Group (RTOG) 9311 phase I study performed by Bradley et al.,[13] in which the estimated rate of grade 3 or more lung toxicity was 0% after IFRT of 70.9 Gy was given in 2.15-Gy once-daily fractions to patients with V20 values of 25% to less than 37%.

The minimal planned total dose was prescribed to be 60 Gy/24 fractions (BED Gy10 is equivalent to that of 62 Gy/31 fractions). The maximum planned total dose was prescribed according to the V20 value as follows: (1) V20 less than 15%, 70 Gy/28 fractions (BED Gy10 is almost equivalent to that of 74 Gy/37 fractions), (2) 15% ≤ V20 < 25%, 67.5 Gy/26 fractions (BED Gy10 is almost equivalent to that of 70 Gy/35 fractions), (3) 25% ≤ V20 < 30%, 65 Gy/26 fractions (BED Gy10 is almost equivalent to that of 68 Gy/34 fractions). The decision regarding the final total dose was made by the radiation oncologist under these dose settings. The details of IFRT given are shown in Table 2.

As the concurrent CHT, weekly intravenous CBDCA (area under the curve [AUC], 1.5–2.0) and PTX (30–35 mg/m^2) during IFRT was set up in principle. This regimen and the dose setting were considered based on the findings of a phase I study performed by Ohashi et al.,[14] which defined the dose level of CBDCA (AUC, 2.0) and PTX (35 mg/m^2) in combination with hyperfractionated RT (69.6 Gy in 1.2-Gy twice-daily fractions) with ENI as the maximum tolerated dose. Details of the CHT given are shown in Table 2.

The tumor response rate was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines as follows: complete response (CR), the disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the longest diameters of target lesions, taking as a reference the baseline longest diameter sum; progressive disease (PD), at least a 20% increase in the sum of the longest diameters of target lesions, taking as

Table 2. Details of treatment for each patient

Patient no.	Location of primary tumor	Involved-field radiation therapy				Concurrent chemotherapy		
		CTV (cc)	V20 (%)	OTT (days)	TD (Gy)	CBDCA (AUC)	PTX (mg/m^2)	Total no. of courses
1	Rt. LL	47.4	28.0	37	65	2	35	6
2	Rt. UL	65.5	21.4	37	67.5	1.5	30	6
3	Lt. UL	28.3	29.0	36	55	2	35	5
4	Lt. UL	37.1	19.0	37	65	2	30	4
5	Rt. LL	77.7	8.0	40	70	2	30	6
6	Lt. LL	86.7	28.0	37	65	2	35	4
7	Lt. UL	33.4	8.4	40	70	2	30	5
8	Rt. UL	64.2	18.8	33	62.5	1.5	30	5
9	Lt. UL	137.3	16.1	37	65	1.5	30	6
10	Rt. UL	52.6	26.7	38	70	1.5	30	5
Median	–	58.4	20.2	37	65	–	–	5

CTV, clinical target volume; V20, percent total lung volume exceeding 20 Gy; TD, total dose; OTT, overall treatment time; CBDCA, carboplatin; AUC, area under the curve; PTX, paclitaxel

a reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum of the longest diameters since the treatment started.

In-field and out-of-field recurrences were assessed using varying combinations of radiological assessment. In-field recurrence was defined as an increase in radiologic abnormality within the irradiated volume that was not considered to be radiation-induced scarring or radiation pneumonitis. Elective nodal failure (ENF) was defined as recurrence in any lymph node region that was initially uninvolved, in the absence of in-field recurrence.

Acute and late toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). Acute toxicity was defined as that occurring within 90 days of treatment initiation, while late toxicity was defined as that occurring beyond 90 days after treatment initiation. During CHT-RT, CHT and RT were to be interrupted for either grade 3 or greater leukopenia or neutropenia or thrombopenia, and thereafter be resumed when that toxicity had decreased to grade 2 or less. In addition, RT was to be interrupted for grade 3 or greater esophagitis or pneumonitis, and thereafter be resumed when that toxicity had decreased to grade 2 or less.. In addition, the treatment was to be canceled if grade 4 or greater severe toxicity occurred.

The follow-up evaluations were performed at 2-month intervals for the first year, at 3-month intervals for the second year, and at 6-month intervals thereafter. The follow-up evaluation routinely included physical examination, chest X-ray, toxicity assessment, and blood tests. Thoracic-abdominal CT scans were performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. A restaging with head MRI and bone scintigraphy was performed at 6-month intervals after the first half year. The actuarial curves of OAS and the in-field tumor control rates were calculated using the Kaplan-Meier method, with the day of treatment as the starting point.

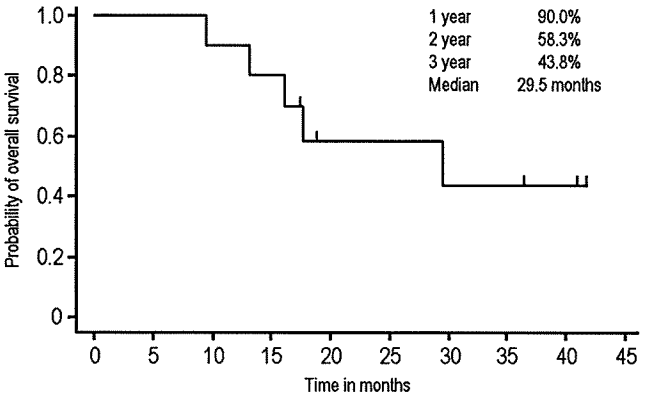

Fig. 2. Overall survival of patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent carboplatin/paclitaxel (CBDCA/PTX)

Results

Tumor response, overall survival, and in-field tumor control

Of the ten patients, one achieved a CR (10.0%), and nine achieved a PR (90.0%) with a tumor response rate of 100%. The final analysis was performed 17 months after the registration of the last patient. At a median follow up of 18.2 months (range, 9.6–41.9 months), five patients (50.0%) had died at the time of the last follow up. The MST was 29.5 months, and the 1-, 2-, and 3-year OAS rates were 90.0%, 58.3%, and 43.8%, respectively (Fig. 2). A median time to in-field tumor progression of 18.1 months was obtained, and the 1-, 2-, and 3-year in-field tumor control rates were 60.0%, 45.0%, and 45.0%, respectively (Fig. 3).

Toxicity

The acute treatment-related toxicities are shown in Table 3. No hematological toxicities of grade 3 or worse were

Table 3. Acute treatment-related toxicities

Toxicity	Grade[a]				
	1	2	3	4	5
Hematological					
Leukocytopenia	1	5	0	0	0
Neutropenia	3	3	0	0	0
Thrombocytopenia	1	1	0	0	0
Anemia	4	1	0	0	0
Nonhematological					
Esophagitis	3	4	0	0	0
Pneumonitis	2	0	0	0	0
Dermatitis	1	0	0	0	0
Fever	1	0	0	0	0
Fatigue	1	0	0	0	0

[a] Common Terminology Criteria for Adverse Events, version 3.0

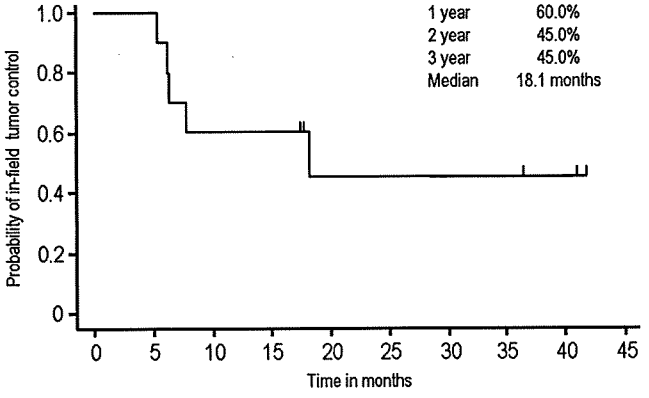

Fig. 3. In-field tumor control in patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent CBDCA/PTX

Table 4. Relationship of acute toxicity, tumor factors, and involved-field radiation therapy (IFRT) factors according to total dose

Total dose	67.5–70 Gy (n = 4)		<67.5 Gy (n = 6)	
	No.	(%)	No.	(%)
Toxicity				
Esophagitis grade 1	1	(25.0)	2	(33.3)
Esophagitis grade 2	0	(0.0)	4	(66.7)
Pneumonitis grade 1	1	(25.0)	1	(16.7)
Tumor factors				
T1–2	2	(50.0)	5	(83.3)
T3	0	(0.0)	0	(0.0)
T4	2	(50.0)	1	(16.7)
N0–1	1	(25.0)	1	(16.7)
N2	1	(25.0)	1	(16.7)
N3	2	(50.0)	4	(66.7)
IFRT factors	Median		Median	
Clinical target volume (CTV; cc)	59.1		55.8	
V20	14.9%		23.5%	

Table 5. Patterns of failure

Recurrences	Patients (n = 10)	
	No.	(%)
None	3	(30.0)
Exclusively in-field	0	(0.0)
In-field and elective nodes	0	(0.0)
In-field and distant	4	(40.0)
In-field, elective nodes, and distant	1	(10.0)
Elective nodes only without in-field elective noda failure (ENF)	0	(0.0)
Distant only without in-field	2	(20.0)

observed. No acute nonhematological toxicities of grade 3 or worse, including radiation esophagitis and radiation pneumonitis, were observed. With a median follow-up time of 36 months for the five surviving patients, only grade 1 pneumonitis/pulmonary infiltrates, in three patients, and grade 1 fibrosis of the subcutaneous tissue, in one patient, were observed as late toxicities. No late grade 2 or worse toxicities were observed. Therefore, no overall toxicity of grade 3 or worse was observed. The relationships regarding toxicity, tumor factors, and IFRT factors according to total dose are summarized in Table 4. There was no difference in the CTV value between the patients who were irradiated with a total dose of less than 67.5 Gy and those who were irradiated with a total dose of 67.5–70 Gy. However, the percentage of those with grade 2 esophagitis was higher in the group with less than 67.5 Gy in comparison to the group with a total dose of 67.5–70 Gy.

Patterns of failure

The patterns of failure are shown in Table 5. Of the ten patients, three (30.0%) were disease-free at the last follow up, and disease recurrences manifested in seven patients (70.0%). In-field recurrences occurred in five patients (50.0%), and out-of-field recurrences were seen in seven patients (70.0%). No ENF was observed. However, regional out-of-field recurrence was observed in one patient who had an in-field recurrence and lung metastasis, this patient had a supraclavicular recurrence in a T2N3 (the primary tumor was located in the left upper lobe). The relationships of the patterns of failure, prognosis, tumor factors, and IFRT factors according to total dose are summarized in Table 6. No in-field recurrences occurred in the four patients who were irradiated with a total dose of 67.5–70 Gy, and three had no evidence of disease (NED). On the other hand, in-field recurrences occurred in five (83.3%) of the six patients who were irradiated with a total dose of less than 67.5 Gy; no patients had NED, and five died of the disease.

Treatment delivery

Nine of the ten patients (90%) received a higher dose than the minimum planned total dose of 60 Gy that was prescribed in the protocol. One patient (patient 3), who received less than 60 Gy of IFRT had T2N3 disease with multiple contralateral mediastinal nodes. In the course of therapy, this patient had grade 2 esophagitis, and volunteered to stop the treatment when the total dose reached 55 Gy. In three

Table 6. Relationship of patterns of failure, prognosis, tumor factors, and IFRT factors according to total dose

Total dose	67.5–70 Gy ($n = 4$)		<67.5 Gy ($n = 6$)	
	No.	(%)	No.	(%)
Patterns of failure				
In-field recurrence	0	(0.0)	5	(83.3)
Elective nodal failure (ENF)	0	(0.0)	0	(0.0)
Distant metastasis	1	(25.0)	4	(66.7)
Prognosis				
No evidence of disease (NED)	3	(75.0)	0	(0.0)
Alive with disease (AWD)	1	(25.0)	1	(16.7)
Died of disease (DOD)	0	(0.0)	5	(83.3)
Tumor factors				
T1–2	2	(50.0)	5	(83.3)
T3	0	(0.0)	0	(0.0)
T4	2	(50.0)	1	(16.7)
N0–1	1	(25.0)	1	(16.7)
N2	1	(25.0)	1	(16.7)
N3	2	(50.0)	4	(66.7)
IFRT factors	Median		Median	
Clinical target volume (CTV; cc)	59.1		55.8	
V20	14.9%		23.5%	

patients (patients 4, 8, and 9; patient numbers in Tables 1 and 2) IFRT was completed with a smaller dose than the maximum planned dose, according to the judgment of the radiation oncologist. Incidentally, patients 4 and 8 had N3 disease that had a wide regional spread in the mediastinum, and patient 9 had T4N1 disease whose primary tumor, which had a wide spread, lay adjacent to the esophagus. In these three patients, grade 2 esophagitis developed during the treatment period. Therefore, the radiation oncologist worried that the esophagitis would worsen, and these patients completed treatment with a lower dose than the maximum planned dose.

Discussion

The treatment results of conventional RT for NSCLC have not been satisfactory; therefore, many therapeutic strategies to improve the treatment results have been attempted so far. In stage I NSCLC, stereotactic body radiotherapy (SBRT) has been performed recently, and excellent local control rates, of more than 90%, and OAS of 70%–80%, which matched the results from surgical resection, were reported.[15–17] We anticipate that SBRT is going to be recognized as a choice for the alternative treatment of stage I NSCLC. In contrast, in locally advanced NSCLC, the standard treatment in the past 20 years has changed dramatically, providing better results. The current standard treatment for locally advanced NSCLC is recognized to be concurrent CHT-RT, but the results provided by concurrent CHT-RT are not entirely satisfactory. Moreover, the optimal details for RT, such as CTV delineation and the irradiated field remain unclear. For many years, it has been thought that standard RT typically entails delivering 40 Gy of ENI to the ipsilateral hilum, the whole mediastinum, and occasionally the supraclavicular fossa even without evidence of disease in these areas, followed by a 20-Gy boost to the GTV.[18] However, it is never easy to irradiate with a high total dose using this irradiation technique with ENI, because the incidence of severe radiation esophagitis and pneumonitis increases with increases in the total dose and ENI has not been shown to be effective.

Recently, IFRT in which ENI is omitted to achieve an improvement in the local control by high-dose irradiation without increasing the toxicity, has been attempted for locally advanced NSCLC.[8–10,13,19–24] As a result, the possibility of prolongation of the MST and reduction in severe toxicity has been reported, and a low incidence of ENF after IFRT has also been shown. Table 7 lists the results of IFRT trials for NSCLC. At present, 74 Gy in 2-Gy fractions is considered to be the recommended dose setting for IFRT with concurrent weekly CBDCA/PTX for locally advanced NSCLC, according to the results of several phase I and II studies, and it was reported that this treatment provided MSTs of 22–37 months.[22–25] Furthermore, the RTOG 0617 trial, a randomized phase III study, comparing standard dose (60 Gy) versus high-dose (74 Gy) 3DCRT or intensity-modulated radiation therapy (IMRT) without ENI with concurrent and consolidation CBDCA/PTX for locally advanced NSCLC. is currently underway. Accordingly, many radiation oncologists are interested in the efficacy of IFRT with concurrent CBDCA/PTX. However, in Japan, no clinical trial of this treatment has yet been performed. Therefore, we consider that a feasibility study of IFRT with concurrent CBDCA/PTX is worth performing in Japan.

In the present preliminary study, the MST and the 1-, 2-, and 3-year OAS in ten patients who were treated with hypofractionated IFRT in once-daily fractions of 2.5 Gy with concurrent weekly CBDCA/PTX were 29.5 months, 90.0%, 58.3%, and 43.8%, respectively. In addition, no ENF and no grade 3 or worse radiation esophagitis was observed. Moreover, no grade 3 or worse radiation pneumonitis was observed, although the primary site in 70% of the patients was located in the upper lobe, whose risk of pneumonitis is lower than that of the lower lobe. Considering these results, hypofractionated IFRT in once-daily fractions of 2.5 Gy with concurrent weekly CBDCA/PTX is therefore considered to be a feasible and safe irradiation method to increase the total dose without increasing the occurrence of either severe radiation esophagitis or pneumonitis, while also demonstrating a low rate of ENF. In addition, hypofractionated IFRT with a high total dose of 67.5 Gy or more may be a promising modality for improving in-field tumor control and prolonging the OAS. However, we think that a small CTV in the mediastinum may be one of the conditions that will allow us to irradiate patients safely at a high dose. Though the irradiated field is certainly small in IFRT in comparison to the general RT field with ENI, the irradiated volume of the esophagus is never small in patients with N2–3 disease that has a wide and long spread of lymph node metastasis in the mediastinum. In these patients, due to the large irradiated volume of the esophagus, V20 increases. Therefore, in the present study we determined the total irradiated dose according to the V20 value; it seems that patients with a narrow spread of mediastinal lymph node

Table 7. Summary of involved-field radiation therapy for non-small-cell lung cancer

Author/Trial (year)	Trial type	No. of patients	Stage	CHT Regimen	Timing of CHT	Fraction size (Gy)	Radiation dose (Gy)	MST (months)	% Acute grade 3/4		% ENF
									Esophagitis	Pneumonitis	
Rosenzweig[19] (2007)	–	524	I–III (III: 65%)	CDDP-based	SEQ/CON (41%/15%)	1.8–2	66	21	NR	NR	6
Yuan[20] (2007)	PRT	98	III	CDDP ETP	CON (100%)	2	68–74	20	4	1	7
DDHK 97–11[8] (2002)	PII	50	III	CBDCA PTX	SEQ (100%)	2	70	18	2	0	0
RTOG 9311[21] (2005)	PI/II	177	I–III (III: 47%)	NR	SEQ (14%)	2.15	(V20 < 25%)				
							70.9–83.8	NR	0	0	
							90.3		0	9	
							(25% ≤ V20 < 37%)				7
							70.9	NR	0	0	
							77.4		0	8	
RTOG L-0117[22]				CBDCA PTX	CON (100%)		(V20 ≤ 30%)				
(2005)	PI	17	I–III			2.15	75.25	NR	0	12	NR
		9				2	74		11	0	
	PII	24				2	74	22[b]			
NCCTG 0028[23] (2006)	PI	13	I–III (III: 69%)	CBDCA PTX	CON (100%)	2	(V20 < 40%)				
							70	NR	0	0	
							74		0	17	0
							78		0	50	
						2	74	37[b]			
CALGB 30105[24] (2008)	PII	42	III	CBDCA PTX	CON (93%)	2	74[a]	24	16	16	NR

DDHK, Daniel den Hoed Kliniek; RTOG, Radiation Therapy Oncology Group; NCCTG, North Central Cancer Treatment Group; CALGB, Cancer and Leukemia Group B; PRT, prospective randomized trial; CHT, chemotherapy; CDDP, cisplatin; ETP, etoposide; NR, not reported; CBDCA, carboplatin; PTX, paclitaxel; SEQ, sequential; CON, concurrent; MST, median survival time; ENF, elective nodal failure; P, phase; V20, percent total lung volume exceeding 20 Gy

[a] Slightly wide involved-field radiation therapy with limited elective nodal irradiation

[b] Data from reference 25

metastases could therefore receive a high total dose. As a result, good in-field control and a low rate of esophagitis were achieved in the patients who received a total dose of 67.5–70 Gy.

In the RTOG 0117 phase I study, three of the initial eight patients treated with 75.25 Gy in 2.15-Gy daily fractions with weekly CBDCA/PTX developed dose-limiting pulmonary toxicity. Therefore, it was concluded that the toxicity of the high total dose with the high fractional dose and concurrent CHT exceeded the safety limit. The phase II portion of RTOG 0117 is now underway to accrue patients at the de-escalated dose level of 74 Gy in 2-Gy daily fractions. Nevertheless, we consider that 75.25 Gy in 2.15-Gy fractions may still be a safe dose fractionation with concurrent CHT, if the total lung V20 values are set at less than 25%, instead of 30% or less, in regard to the eligibility criteria of patients to undergo the RTOG 0117 trial. In the near future we are planning to design a dose-escalation study of hypofractionated IFRT, given in 2.5-Gy fractions with concurrent weekly CBDCA/PTX, for patients with total lung V20 values of less than 25%.

Conflict of interest statement

No author has any conflict of interest.

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ORIGINAL ARTICLE

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National structure of radiation oncology in Japan with special reference to designated cancer care hospitals

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Abstract

Background. The structure of radiation oncology in designated cancer care hospitals in Japan was investigated in terms of equipment, personnel, patient load, and geographic distribution, and compared with the structure in other radiotherapy facilities.

Methods. The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) conducted a questionnaire survey about the national structure of radiation oncology in 2005. In the current study, the structures of 326 designated cancer care hospitals and the other 386 radiotherapy facilities in Japan were compared.

Results. Designated cancer care hospitals accounted for 45.3% of all radiotherapy facilities. The patterns of equipment and personnel in designated cancer care hospitals and the other radiotherapy facilities were as follows: linear accelerators/facility, 1.2 and 1.0; dual-energy function, 73.1% and 56.3%; three-dimensional conformal radiotherapy function, 67.5% and 52.7%; intensity-modulated radiotherapy function, 30.0% and 13.9%; annual number of patients/linear accelerator, 289.7 and 175.1; ^{192}Ir remote-controlled afterloading systems, 27.6% and 8.6%; and average number of full-time equivalent radiation oncologists/facility, 1.4 and 0.9 ($P < 0.0001$). There were significant differences in equipment and personnel between the two types of facilities. Annual patient loads/full-time equivalent radiation oncologist in the designated cancer care hospitals and the other radiotherapy facilities were 252 and 240. Geographically, the number of designated cancer care hospitals was associated with the population, and the number of JASTRO-certified physicians was associated with the number of patients undergoing radiotherapy.

Conclusion. The Japanese structure of radiation oncology in designated cancer care hospitals was more mature than that in the other radiotherapy facilities in terms of equipment, although a shortage of personnel still exists. The serious understaffing problem in radiation oncology should be corrected in the future.

Key words Radiotherapy · Medical Engineering · Epidemiology

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Introduction

In Japan, the Cancer Control Act was implemented in 2007 in response to patients' urgent petitions to the government. This law strongly advocates the promotion of radiotherapy (RT) and an increase in the number of radiation oncologists (ROs) and medical physicists. At the same time, the Ministry of Health, Labour and Welfare began the accreditation of "designated cancer care hospitals" with the aim of correcting regional differences in the quality of cancer care and strengthening cooperation among regional cancer care hospitals. The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) has conducted national structure surveys of RT facilities in Japan every 2 years since 1990.[1] The structure of radiation oncology in Japan has improved in terms of equipment and functions in accordance with the increasing number of cancer patients who require RT. Public awareness of the importance of RT is gradually expanding due to the above law. We introduced Patterns of Care Study (PCS) in Japan in 1996; these studies have been carried out every 4 years and have disclosed significant differences in the quality of RT according to the types of facilities and their caseloads.

In the present study, the structure of radiation oncology in designated cancer care hospitals in Japan was investigated in terms of equipment, personnel, patient load, and geographic distribution, and compared with these features of other RT facilities in Japan.

Materials and methods

JASTRO carried out a national structure survey of radiation oncology in 2005, in the form of a questionnaire, between March 2006 and February 2007.[2,3] The questionnaire consisted of questions about the number of treatment machines and modality by type, the number of personnel by job category, and the number of patients by type and the disease site. The response rate was 712 of 735 (96.9%) from all actual RT facilities in Japan.

The number of facilities certified by the Ministry of Health, Labour and Welfare as designated cancer care hospitals by the end of fiscal 2007 was 351. Of the total 351 facilities, 47 were designated prefectural cancer care hospitals and 304 were designated regional cancer care hospitals. Three hundred and fifty-three facilities, including the National Cancer Center Hospital and the National Cancer Center Hospital East were included in this group as designated cancer care hospitals. Seven facilities did not return the survey data, and 20 facilities did not have departments of RT at that point in the survey. The structures of 326 designated cancer care hospitals and the other 386 RT facilities were then analyzed. SAS 8.02[4] (SAS Institute, Cary, NC, USA) was used for the statistical analysis. The statistical significance was tested by means of a χ^2 test, Students' *t*-test, or analysis of variance (ANOVA).

The Japanese Blue Book guidelines[5] were used as the standard of comparison with the results of this study. These guidelines show the guidelines for the structure of radiation oncology in Japan based on PCS data.[5,6] The standard guidelines for annual patient load/external beam equipment were set at 250–300 (warning level 400); those for annual patient load /full-time equivalent (FTE) radiation oncologist (RO) were set at 200 (warning level 300), and those for annual patient load /FTE RT technologists at 120 (warning level 200).[5,6]

Results

Current situation of radiation oncology in designated cancer care hospitals and the other RT facilities in Japan

Table 1 shows the numbers of new patients and total numbers of patients (new plus repeats) requiring RT in 2005 at the total number of surveyed designated cancer care hospitals and other RT facilities in Japan ($n = 712$). Designated cancer care hospitals accounted for 45.3% (333/735) of all the RT facilities in Japan. The numbers of new patients and total numbers of patients in all the RT facilities in Japan were estimated at approximately 162 000 (156 318*735/712) and 198 000 (191 173*735/712), respectively (see Table 1 footnote). In designated cancer care hospitals, the corresponding numbers of patients were approximately 99 000 (96 558*333/326) and 121 000 (118 548*333/326), respectively (see Table 1 footnote). The number of patients in designated cancer care hospitals accounted for 61.1% of the number of patients in all RT facilities, for both new patients and the total number of patients (99 000/162 000 and 121 000/198 000; see Table 1 footnote). The average numbers of new patients/facility were 296.2 for designated cancer care hospitals and 154.8 for the other RT facilities, respectively ($P < 0.0001$). For the average numbers of total

Table 1. The numbers of new patients and total patients (new plus repeat) requiring radiotherapy (RT) in designated cancer care hospitals and the other RT facilities

	Designated cancer care hospitals	Other RT facilities	*P* value	Total
Facilities	326	386		712
New patients	96558[a]	59760		156318[b]
Average no. new patients/facility	296.2	154.8	<0.0001	219.5
Total patients (new + repeat)	118548[a]	72625		191173[b]
Average no. total patients/facility	363.6	188.1	<0.0001	268.5

[a]The number of designated cancer care hospitals with RT was 333, and the number of new patients in designated cancer care hospitals was estimated at approximately 99000 (96558*333/326); the corresponding number of total patients (new plus repeat) was 121000 (118548*333/326)
[b]The number of RT facilities was 735 in 2005, and the number of new patients was estimated at approximately 162000 (156318*735/712); the corresponding number of total patients (new plus repeat) was 198000 (191173*735/712)

patients/facility, the corresponding data were 363.6 and 188.1, respectively ($P < 0.0001$).

Table 2 shows the equipment patterns, staffing patterns, and patient loads in designated prefectural cancer care hospitals and designated regional cancer care hospitals. There were significant differences in the average number of linear accelerators (Linacs)/facility, the ownership of the intensity-modulated RT (IMRT) function of the Linac, the average number of patients/facility, the average number of patients/Linac, the number of ^{192}Ir remote-controlled afterloading systems (RALSs) ($P < 0.0001$), and the number of computed tomography (CT) simulators in the two types of facilities ($P = 0.0015$). The IMRT function does not necessarily mean its actual use in 2005, but its availability as equipment. The average numbers of FTE ROs/facility were 3.1 for designated prefectural cancer care hospitals and 1.2 for designated regional cancer care hospitals ($P < 0.0001$). The average numbers of JASTRO-certified physicians/facility were 2.1 and 0.7 ($P < 0.0001$).

Facility and equipment patterns and patient load/Linac in designated cancer care hospitals and the other RT facilities

Table 3 shows the RT equipment patterns and related functions in the designated cancer care hospitals and the other RT facilities. In the designated cancer care hospitals, 397 Linacs, 7 telecobalt machines, 17 Gamma Knife machines, 46 ^{60}Co RALSs, and 91 ^{192}Ir RALSs were actually used. In the other RT facilities, the corresponding data were 368, 4, 31, 18, and 28, respectively. The ownership of equipment in designated cancer care hospitals, excluding telecobalt machines and Gamma Knife machines, was significantly higher than that in the other RT facilities (Linac, $P = 0.0002$; other equipment, $P < 0.0001$). In designated cancer care hospitals, the Linac system used dual-energy function in 291 systems (73.1%), three-dimensional conformal RT function (3DCRT) in 268 (67.5%), and IMRT function in 119 (30.0%). In the other RT facilities, the corresponding data

Table 2. Equipment patterns, staffing patterns, and patient loads in designated prefectural cancer care hospitals and designated regional cancer care hospitals

	Designated prefectural cancer care hospitals ($n = 49$)		Designated regional cancer care hospitals ($n = 277$)		*P* value
	n	%	*n*	%	
Linac	87	100.0[a]	310	95.7[a]	0.1377
With IMRT function	46	52.9[b]	73	23.5[b]	<0.0001
No. Linacs/facility	1.8		1.1		<0.0001
Annual no. patients/facility	722.3		300.2		<0.0001
Annual no. patients/Linac	406.8[c]		257.0[c]		<0.0001
^{192}Ir RALS (actual use)	37	75.5	54	8.6	<0.0001
No. of CT simulators	47	83.7[c]	170	59.9[c]	0.0015
Average no. of FTE ROs/facility	3.1		1.2		<0.0001
Average no. of JASTRO-certified ROs/facility	2.1		0.7		<0.0001

Linac, Linear accelerator; IMRT, intensity-modulated RT; RALS, remote-controlled afterloading system; CT, computed tomography; FTE, full-time equivalent (40 h/week only for RT practice); RO, radiation oncologist; JASTRO, Japanese Society of Therapeutic Radiology and Oncology

[a]Percentage calculated from the number of systems using this function and the total number of Linac systems

[b]Percentage calculated from the number of patients and the number of Linac systems. Facilities without Linacs were excluded from the calculation

[c]Percentage of facilities which have equipment

Table 3. Equipment, its function, and patient load per equipment in designated cancer care hospitals and the other RT facilities

	Designated cancer care hospitals ($n = 326$)		Other RT facilities ($n = 386$)		*P*-value	Total ($n = 712$)	
	n	%	*n*	%		*n*	%
Linac	397	96.3[a]	368	88.9[a]	0.0002	765	92.3[a]
With dual-energy function	291	73.1[b]	207	56.3[b]	<0.0001	498	65.1[b]
With 3D-CRT function (MLC width =<1.0 cm)	268	67.5[b]	194	52.7[b]	<0.0001	462	60.4[b]
With IMRT function	119	30.0[b]	51	13.9[b]	<0.0001	170	22.2[b]
Average no. Linacs/facility	1.2		1.0		<0.0001	1.1	
Annual no. patients/Linac	289.7[c]		175.1[c]		<0.0001	234.6[c]	
Telecobalt (actual use)	18 (7)		16 (4)			34 (11)	
Gamma Knife	17		31		0.1400	48	
^{60}Co RALS (actual use)	51 (46)	15.6 (14.1)	23 (18)	7.1[c] (5.5)	<0.0001	74 (64)	10.4[c] (9.0)
^{192}Ir RALS (actual use)	94 (91)	28.5[c] (27.6)	29 (28)	8.9[c] (8.6)	<0.0001	123 (119)	17.1[c] (16.6)

3D-CRT, three-dimensional conformal RT; other abbreviations as in Table 2

[a]Percentage of facilities which have this equipment (two or more pieces of equipment per facility)

[b]Percentage calculated from the number of systems using this function and the total number of Linac systems

[c]Percentage calculated from the number of patients and the number of Linac systems. Facilities without Linacs were excluded from the calculation

were 207 (56.3%), 194 (52.7%), and 51 (13.9%), respectively. The functions of Linac showed significant superiority, approximately 15% greater, in designated cancer care hospitals compared with the other RT facilities ($P < 0.0001$). The patient loads/Linac were 289.7 for designated cancer care hospitals and 175.1 for the other RT facilities ($P < 0.0001$). Fig. 1 shows the distribution of annual patient load/Linac in designated cancer care hospitals and the other RT facilities. Eighteen percent of designated cancer care hospitals and 6% of the other RT facilities were subject to treatment that exceeded the warning level of the Japanese Blue Book Guidelines,[5] of 400 patients/Linac. However, the average patient load/Linac in the other RT facilities was less than the guideline level.

Table 4 shows the RT planning and other equipment patterns. X-ray simulators were installed in 79.1% of the designated cancer care hospitals and 61.7% of the other RT facilities. CT simulators were installed in 63.5% and 48.4%, respectively. A noteworthy difference was found between designated cancer care hospitals and the other RT facilities in the rate of X-ray simulator and CT simulator installation ($P < 0.0001$). Only a very few facilities owned magnetic resonance imaging (MRI) equipment for the RT department, although computer use for RT recording was pervasive in both designated cancer care hospitals and the other RT facilities.

Staffing patterns and patient loads in designated cancer care hospitals and the other RT facilities

Table 5 shows the staffing patterns and patient loads in designated cancer care hospitals and the other RT facilities. We found that 50.3% of the designated cancer care hospitals and 31.9% of the other RT facilities had their own designated RT beds, and ROs also had to care for their inpatients. The total numbers of FTE ROs were 471.3 for the designated cancer care hospitals and 303.2 for the other RT facilities. The average numbers of FTE ROs/facility were 1.4 and 0.9, respectively ($P < 0.0001$). The patient loads/FTE RO were 251.5 and 239.6. Fig. 2 shows the distribution of annual patient load/FTE RO in designated cancer care hospitals and the other RT facilities. Twenty-four percent of designated cancer care hospitals and 11% of the other RT facilities treated more than 300 patients/RO, which exceeded the warning level of the Japanese Blue Book Guidelines.[5] Fig. 3 shows the percentage of facilities by patient load/FTE RO. The largest number of facilities featured a patient/FTE RO level in the 150–199 range for designated cancer care hospitals and in the 100–149 range for the other RT facilities. The second largest numbers featured patient/FTE RO levels in the 200–249 and 50–99 ranges, respectively. Facilities that had less than 1 FTE RO

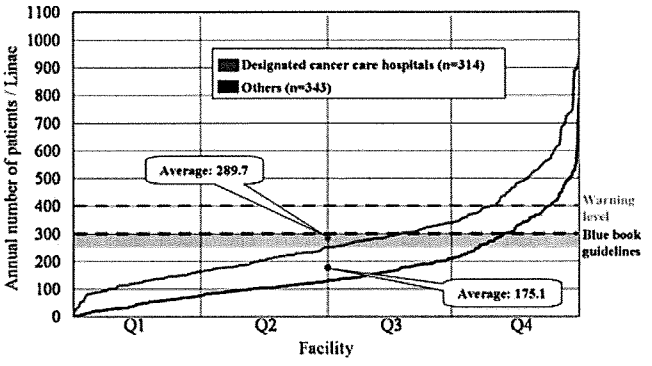

Fig. 1. Distribution of annual patient load/linear accelerator (*Linac*) in designated cancer care hospitals and the other radiotherapy (RT) facilities (*others*). *Horizontal axis* represents facilities arranged in order of increasing annual number of patients/Linac within facilities. The above-mentioned facilities are divided in quaters; *Q1*, 0%–25%; *Q2*, 26%–50%; *Q3*, 51%–75%; *Q4*, 76%–100%

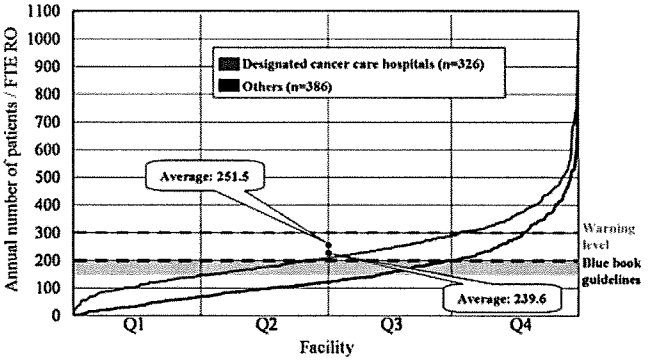

Fig. 2. Distribution of annual patient load/ full-time equivalent radiation oncologist (*FTE RO*) in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual numbers of patients / FTE RO within facilities. The number of FTE ROs for facilities with less than one FTE was calculated as FTE = 1 to avoid overestimating patient load / FTE RO. *Q1-Q4*, as in Fig. 1 legend

Table 4. Radiotherapy planning and other equipment in designated cancer care hospitals and the other RT facilities

	Designated cancer care hospitals ($n = 326$)		Other RT facilities ($n = 386$)		*P*-value	Total ($n = 712$)	
	n	%	*n*	%		*n*	%
X-ray simulator	262	79.1[a]	240	61.7[a]	<0.0001	502	69.7[a]
CT simulator	217	63.5[a]	190	48.4[a]	<0.0001	407	55.3[a]
RTP computer (>= 2)	510 (101)	96.3[a] (38.5)	430 (45)	90.4[a] (11.7)	0.0019 (<0.0001)	940 (146)	93.1[a] (20.5)
MRI (>= 2)	588 (203)	97.5[a] (77.5)	524 (135)	92.2[a] (35.0)	0.0017 (<0.0001)	1112 (338)	94.7[a] (47.5)
For RT only	6	1.8[a]	6	1.6[a]	–	12	1.7[a]
Computer use for RT recording	298	91.4[a]	328	85.0[a]	0.0086	626	87.9[a]

RTP, RT planning; MRI, magnetic resonance imaging; RT, radiotherapy; other abbreviations as in Table 2
[a] Percentage of institutions which have equipment (two or more pieces of equipment per institution)

Table 5. Staffing patterns and patient loads in designated cancer care hospitals and the other RT facilities

	Designated cancer care hospitals (n = 326)	Other RT facilities (n = 386)	P-value	Total (n = 712)
Facilities with RT beds	164 (50.3)	123 (31.9)		287 (40.3)
Average no. RT beds/facility	4.8	3.0	0.0001	3.6
Total (full-time + part-time) FTE ROs	471.3	303.2		774.5
Average no. FTE ROs/facility	1.4	0.9	<0.0001	1.1
No. of JASTRO-certified ROs (full-time)	293	133		426
Average no. JASTRO-certified ROs/facility	0.9	0.4	<0.0001	0.6
Patient load/FTE RO	251.5	239.6	0.0641	246.8
Total no. of RT technologists	889.9	744.6		1634.5
Average no. of RT technologists/facility	2.7	2.3	<0.0001	2.3
Patient load/RT technologist	133.2	97.5	<0.0001	117.0
Full-time medical physicists + part-time	65.0 + 17.1	52.0 + 13.0		117.0 + 30.1
Full-time RT QA staff + part-time	156.0 + 8.0	100.8 + 5.0		256.8 + 13.0
Total no. of nurses/assistants/clerks	476.8	430.2		907.0

Data values in parentheses are percentages
QA, quality assurance; other abbreviations as in Table 2

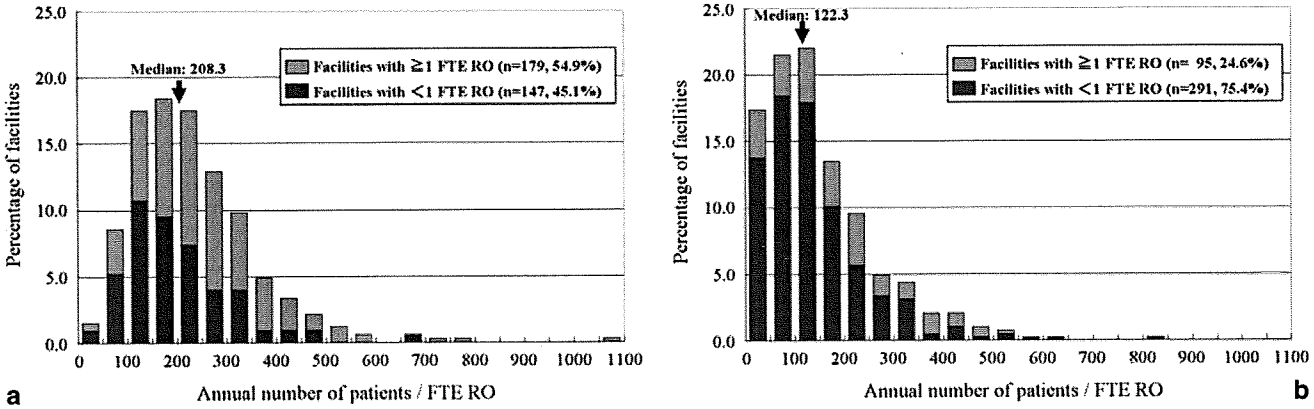

Fig. 3. **a** Percentage of facilities by patient load / FTE RO in designated cancer care hospitals. *Each bar* represents an interval of 50 patients per FTE RO. The number of FTE ROs for facilities with less than one FTE was calculated as FTE = 1 to avoid overestimating patient load / FTE RO. **b** Percentage of facilities by patient load / FTE RO in the other RT facilities. *Each bar* represents an interval of 50 patients per FTE RO. The number of FTE ROs for facilities with less than one FTE was calculated as FTE = 1 to avoid overestimating patient load / FTE RO

still accounted for about 45.1% of designated cancer care hospitals and 75.4% of the other RT facilities.

The total numbers of RT technologists were 889.9 for designated cancer care hospitals and 744.6 for the other RT facilities. The average numbers of RT technologists in the two types of facilities were 2.7 and 2.3, respectively ($P < 0.0001$). The patient loads/RT technologist were 133.2 and 97.5, respectively ($P < 0.0001$). Fig. 4 shows the distribution of annual patient load/RT technologist in designated cancer care hospitals and the other RT facilities. Fourteen percent of designated cancer care hospitals and 8% of the other RT facilities treated more than 200 patients per RT technologist, exceeding the warning level of the Japanese Blue Book Guidelines.[5] Fig. 5 shows the percentage of facilities by patient load/RT technologist. The largest number of facilities featured a patient/RT technologist level in the 80–99 range for both designated cancer care hospitals and the other RT facilities. The second largest numbers featured patient/RT technologist levels in the ranges of 100–119 and 60–79, respectively.

There were 65.0 FT (and 17.1 part-time) medical physicists for designated cancer care hospitals and 52.0 FT (and

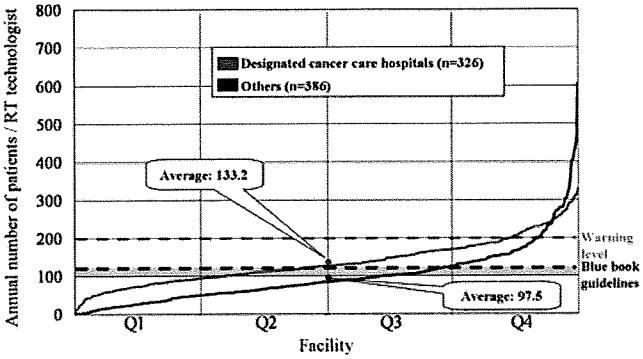

Fig. 4. Distribution of annual patient load / RT technologist in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual number of patients / RT technologist within facilities. *Q1-Q4*, As in Fig. 1 legend

13.0 part-time) medical physicists for the other RT facilities. There were 156.0 FT (and 8.0 part-time) RT quality assurance staff for designated cancer care hospitals and 100.8 FT (and 5.0 part-time) RT quality assurance staff for the other

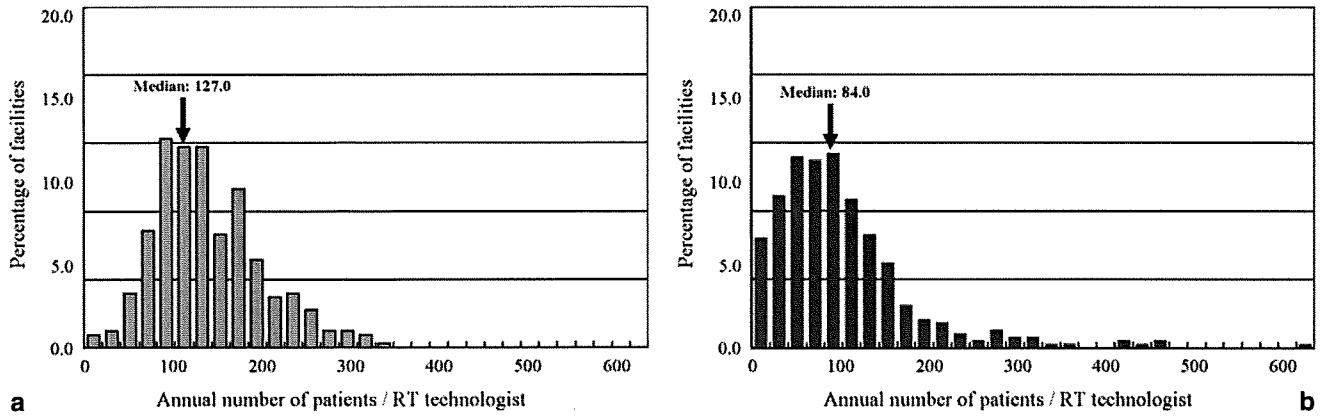

Fig. 5. **a** Percentage of facilities by patient load / RT technologist in designated cancer care hospitals. *Each bar* represents an interval of 20 patients per FTE staff. **b** Percentage of facilities by patient load / RT technologist in the other RT facilities. *Each bar* represents an interval of 20 patients per FTE staff

Table 6. Primary disease sites, and brain metastasis and bone metastasis treated with RT in designated cancer care hospitals and the other RT facilities

Primary site	Designated cancer care hospitals (n = 321)		Other RT facilities (n = 380)		P-value	Total (n = 701)	
	n	%	n	%		n	%
Cerebrospinal	4130	4.3	4469	7.7	<0.0001	8599	5.6
Head and neck (including thyroid)	11199	11.6	5174	8.9	<0.0001	16373	10.6
Esophagus	6647	6.9	3566	6.1	<0.0001	10213	6.6
Lung, trachea, and mediastinum	18097	18.8	11943	20.5	<0.0001	30040	19.4
Lung	15341	15.9	10051	17.3	<0.0001	25392	16.4
Breast	18733	19.4	11528	19.8	0.0458	30261	19.6
Liver, biliary, tract, and pancreas	4116	4.3	2239	3.9	<0.0001	6355	4.1
Gastric, small intestine, and colorectal	4868	5.0	2976	5.1	0.5193	7844	5.1
Gynecologic	6277	6.5	2392	4.1	<0.0001	8669	5.6
Urogenital	11380	11.8	7180	12.4	0.0011	18560	12.0
Prostate	8133	8.4	5085	8.7	0.0291	13218	8.6
Hematopoietic and lymphatic	5499	5.7	2541	4.4	<0.0001	8040	5.2
Skin, bone, and soft tissue	3326	3.4	1878	3.2	0.0223	5204	3.4
Other (malignant)	1165	1.2	910	1.6	<0.0001	2075	1.3
Benign tumors	1033	1.1	1323	2.3	<0.0001	2356	1.5
Pediatric <15 years (included in totals above)	577	0.6	470	0.8	<0.0001	1047	0.7
Total	96470	100.0	58119	100.0	<0.0001	154589[a]	100.0
Metastasis	(n = 326)		(n = 386)		P-value	(n = 712)	
Brain	7212	6.1	8109	11.2	<0.0001	15321	8.0
Bone	16968	14.3	10508	14.5	0.3464	27476	14.4

[a] Total number of new patients was different from this number, because no data on primary sites were reported by some facilities

RT facilities. Finally, there were 476.8 nurses and clerks for designated cancer care hospitals and 430.2 nurses and clerks for the other RT facilities.

Distribution of primary disease sites and palliative treatment in designated cancer care hospitals and the other RT facilities

Table 6 shows the distribution of primary disease sites and palliative treatment in the designated cancer care hospitals and the other RT facilities. The most common disease site in designated cancer care hospitals was the breast; in the other RT facilities, it was lung/bronchus/mediastinum. Head/neck, esophagus, liver/biliary tract/pancreas, gynecologic, hematopoietic/lymphatic, and skin/bone/soft tissue cancers were treated at higher rates at designated cancer care hospitals than at the other RT facilities (skin/bone/soft tissue cancer, $P = 0.0223$; other cancers, $P < 0.0001$). The other RT facilities treated more patients with brain metastasis (11.2% of all new patients) than the designated cancer care hospitals ($P < 0.0001$).

Geographic patterns in designated cancer care hospitals and the other RT facilities

Fig. 6 a,b shows the geographic distribution, for 47 prefectures, of the number of RT facilities arranged in order of increasing population by all prefectures in Japan (Fig. 6a)

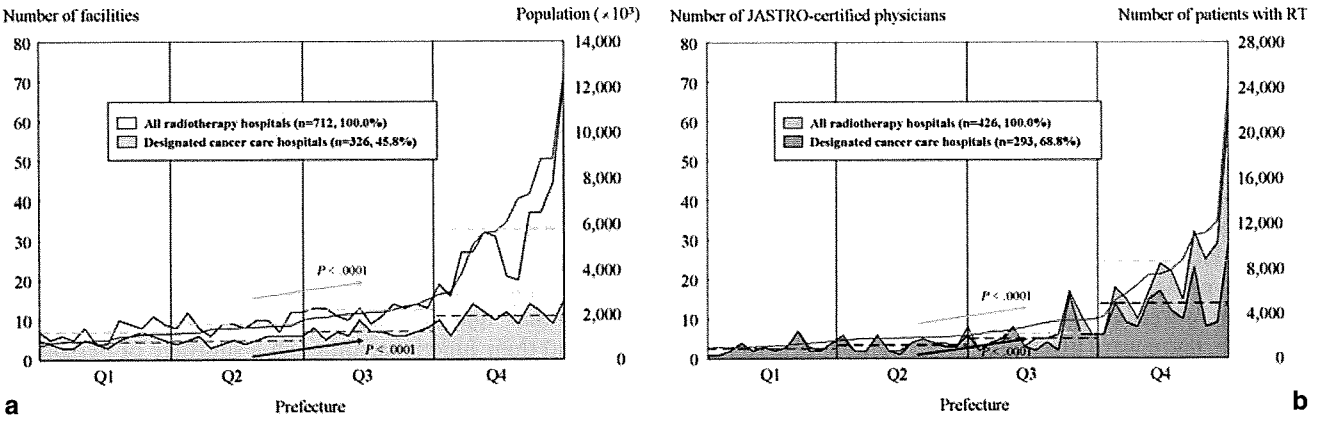

Fig. 6. **a** Geographic distribution, for 47 prefectures, of the number of facilities arranged in order of increasing population. *Upper dashed horizontal bar* shows average number of facilities in the prefectures per 4 separated groups (Q1–Q4) in all RT hospitals, and *lower dashed horizontal bar* shows that number in designated cancer care hospitals. **b** Geographic distribution, for 47 prefectures, of the number of Japanese Society of Therapeutic Radiology and Oncology (*JASTRO*)-certified physicians, arranged in increasing order of the number of patients undergoing RT, by prefecture. *Upper horizontal dashed bar* shows average number of JASTRO-certified physicians in the prefectures per quarter in all RT hospitals, and *lower dashed horizontal bar* shows that number in designated cancer care hospitals. *Q1-Q4*, As in Fig. 1 legend

and the number of JASTRO-certified physicians, arranged in order of increasing number of patients undergoing RT, by all prefectures in Japan (Fig. 6b).[7] The average number of RT facilities per 4 separated groups (Q1–Q4) ranged from 7.2 to 32.9 in all RT facilities in Japan. In designated cancer care hospitals, these numbers ranged from 4.7 to 11.2. There were significant differences in the average number of facilities per quarter in both all RT facilities and in designated cancer care hospitals (both, $P < 0.0001$). The average number of JASTRO-certified physicians per quarter ranged from 2.8 to 24.5 in all RT facilities in Japan. In designated cancer care hospitals, these numbers ranged from 2.8 to 14.0. The average number of JASTRO-certified physicians per quarter showed significant differences in both all RT facilities and designated cancer care hospitals (both, $P < 0.0001$).

Discussion

The number of patients in designated cancer care hospitals was 61.1% of the number of patients (both new patients and the total number of patients) in all RT facilities in Japan, although the designated cancer care hospitals accounted for 45.3% of all RT facilities. About 62 % of all RT facilities have less than 1 FTE RO, while about 45% of designated cancer care hospitals have less than 1 FTE RO. In Japan, the majority of facilities still rely on part-time ROs, especially in the facilities other than the designated cancer care hospitals. The percentage distribution of facilities by patient load/RO in designated cancer care hospitals proved to be largely similar to that of the United States in 1989.[8] However, facilities which have less than 1 FTE RO still account for about 45% of designated cancer care hospitals in Japan. In the United States, all facilities are supported by a full-time RO. The percentage distribution of facilities by patient load/RO in the other RT facilities in the present study was largely similar to that found in Japan in 1990,[8] so a shortage of ROs will remain a major concern in Japan. As for medical physicists, their numbers in Japan are still smaller than those in Europe and the United States. They work mainly in metropolitan areas or academic facilities such as university hospitals or cancer centers. At present, there is no national license for a medical physicist in Japan. Those with a master's degree in science or engineering or radiology technologists with enough clinical experience can take the Japan Radiological Society (JRS)-certified examination to become medical physicists. In Japan, a new educational system is developing to train specialists for cancer care, including medical physicists, medical oncologists, oncology nurses, and palliative care doctors. A sufficient number of RT technologists is ensured, as compared with ROs and medical physicists. However, RT technologists are busy, because they also partly play the role of medical physicists in Japan.

In terms of the distribution of the primary disease site for RT, designated cancer care hospitals treated more patients with head and neck cancers, while the other RT facilities treated more patients with cancers of the lung, trachea, and mediastinum Furthermore, more patients with brain or bone metastasis were treated in the other RT facilities. These results imply that designated cancer care hospitals which treat more potentially curative patients have better structures than the other hospitals.

On a regional basis, the number of all RT facilities and the number of designated cancer care hospitals were strongly associated with population (correlation coefficients were 0.95 and 0.83). These results proved that designated cancer care hospitals were in the appropriate places. However, in some regions where there was a large population, the proportion of designated cancer care hospitals was not sufficient, because many university hospitals were not certified by the Ministry of Health, Labour and Welfare as designated cancer care hospitals. There were two prefectures where the number of RT hospitals was extremely small, as

shown in the Q4 region of Fig. 6a. They were located in metropolitan areas, so many cancer patients who lived in those areas might have received treatment in the hospitals in Tokyo. The numbers of JASTRO-certified physicians in all RT facilities and in the designated cancer care hospitals were also strongly associated with the number of patients undergoing RT (correlation coefficients were 0.92 and 0.83). The JASTRO-certified physicians were in the appropriate places. However, the absolute number of JASTRO-certified physicians was especially insufficient in regions where there were many patients undergoing RT. As shown in Fig. 6b, there were five peaks in the number of JASTRO-certified physicians in the Q3 and Q4 regions. These peaks were Tokyo, Kanagawa, Chiba, Hiroshima, and Gunma, in descending order. In the Tokyo metropolitan area, the Keihanshin area, and the Chukyo area, cancer patients can easily receive treatment at hospitals that are in other regions because these areas are conveniently located in terms of public transpotation (indicated by the jagged graph in Fig. 6b). In Japan, it is necessary to increase the number of designated cancer care hospitals and the number of JASTRO-certified physicians in regions where there is a large population and many patients.

The utilization rate of RT for new cancer patients in Japan remains at about 25% (162 000/660 578[9]), less than half the ratio in the United States and European countries. The "anti-cancer" law was enacted in Japan to promote RT and education for ROs, medical physicists, and other staff members as of April 2007. In Japan, RT is expected to play an increasingly important role because the increase in the elderly population is the highest among other developed countries.

In the present study, the ownership of all equipment was more firmly in place in designated cancer care hospitals than in the other RT facilities.[10] The function of Linac, in particular the IMRT function, does not mean actual use of its function. In 2005, mainly due to severe shortages of personnel, only 6.0% of Linacs with their function were used for actual IMRT in the clinic. The average number of staff members for RT in designated cancer care hospitals was more than that in the other RT facilities. So, the accreditation of designated cancer care hospitals is closely correlated with the maturity of the structures of radiation oncology.[10] However, it is problematic that there are designated cancer care hospitals without their own RT departments. We consider that all the designated cancer care hospitals need to have their own RT departments, because the number of cancer patients requiring RT is rapidly increasing and currently RT in Japan is underutilized compared with that in Europe and the United States. The accreditation of designated cancer care hospitals by the Ministry of Health, Labour and Welfare would be a good start to consolidate RT facilities geographically in Japan.

The structural information on all RT facilities in Japan is regularly surveyed by JASTRO. Although the process and the outcome of cancer care in patients undergoing RT have been investigated by PCS every 4 years, the collection of the outcome information is insufficient. In the United States, a National Cancer Database was established and it has been collecting the data for cancer care. This database is used as the quality indicator for improvements in the processes and outcomes of cancer care. It is necessary to establish an informational system in Japan that can collect national data for cancer care. We have now established a Japanese National Cancer Database based on the RT data. We are preparing the collection of cancer care data by using this system.

In conclusion, the structure of radiation oncology in designated cancer care hospitals in Japan showed maturity, more so than that of other RT facilities, in terms of equipment and their functions, although a shortage of personnel still exists. It is necessary, as national policy, to solve the problem of the arrangement of designated cancer care hospitals and the shortage of personnel for cancer care as clarified by data in this survey.

Conflict of interest

H. Ikeda received a Grant-in-Aid for Cancer Research (No. 18-2) from the Ministry of Health, Labour and Welfare. The other authors have no conflict of interest.

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ORIGINAL ARTICLE

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Comparison of chemotherapy regimens for concurrent chemoradiotherapy in unresectable stage III non-small cell lung cancer

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Abstract
Background. The purpose of this study was to retrospectively compare the survival and toxicities associated with chemoradiotherapy using full-dose and weekly regimens in patients with stage III non-small cell lung cancer.
Methods. Consecutive patients who received concurrent chemoradiotherapy between October 2002 and June 2006 at our institution were enrolled. The prescribed dose for thoracic radiotherapy was 60 Gy in 30 fractions for all the patients.
Results. Fifty-nine patients were enrolled; 36% of the patients were treated with full-dose regimens and 64% with weekly regimens. The patient characteristics were similar in the two groups. In both univariate and multivariate analyses, treatment with weekly regimens was associated with a better overall survival than that with full-dose regimens (2-year survival rates: 75% for weekly regimens vs 41% for full-dose regimens). The toxicities and compliance in the two groups were comparable.
Conclusion. Weekly regimens exhibited more favorable overall survival as compared to full-dose regimens in this retrospective study. Confirmation of the results by a randomized phase III trial is warranted.

Key words Lung cancer · Concurrent chemoradiotherapy · Stage III

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Introduction

Over the past two decades, the most significant advances in the therapy of unresectable stage III non-small cell lung cancer (NSCLC) have been the integration of platinum-based chemotherapy and thoracic radiotherapy.[1,2] Initially, platinum-based induction chemotherapy prior to radiotherapy yielded a prolongation of survival.[3,4] Then, concurrent chemoradiotherapy was found to yield survival superior to that for radiotherapy alone.[5] More recently, concurrent chemoradiotherapy has been demonstrated to increase survival to a greater degree than induction chemotherapy followed by radiotherapy.[6,7] Therefore, concurrent chemoradiotherapy is, at present, considered as the current standard of care for unresectable stage III NSCLC.

In patients with stage IV NSCLC, it has been demonstrated that third-generation agents combined with cisplatin or carboplatin yield superior survival as compared to regimens containing second-generation agents.[8–11] However, these regimens are concurrently administered in reduced doses weekly with thoracic radiotherapy due to their high toxicities.[12] The results of recent randomized trials using weekly reduced-dose regimens, including third-generation agents, for stage III NSCLC have failed to demonstrate superior survival[13,14] as compared to previously published data.[6,7] Furthermore, the results of a randomized trial of cisplatin+etoposide+radiotherapy vs cisplatin+etoposide+radiotherapy consolidation docetaxel failed to demonstrate any benefit of consolidation docetaxel.[15] From these results, one can assume that the standard for concurrent chemoradiation for stage III NSCLC would be the use of full-dose second-generation agent regimens. However, there are no reports of direct comparisons of weekly reduced-dose regimens and full-dose regimens; therefore, the optimal regimen still remains unclear. The purpose of this study was to compare the survival and toxicity in patients with stage III NSCLC treated with full-dose regimens and weekly reduced-dose regimens.

Patients, materials, and methods

Patients

Consecutive patients treated between October 2002 and June 2006 at our institution and satisfying the following eligibility criteria were enrolled for this study. The eligibility criteria were: patients with histologically and/or cytologically diagnosed stage IIIA or IIIB NSCLC with measurable lesions; patient age, 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; weight loss 10% or less during the 3 months before the diagnosis; and no history of previous chemotherapy and/or radiotherapy. The patients were also required to undergo brain magnetic resonance imaging (MRI) or computed tomography (CT) to rule out asymptomatic brain metastasis prior to the start of the study. Patients with malignant pleural effusion and/or contralateral hilar node involvement were not eligible. Some of the patients underwent ^{18}F-fluorodeoxyglucose positron emission computed tomography (PET). All the patients gave written informed consent before the start of the treatment.

Radiotherapy

All the patients were required to undergo chest computed tomography (CT) to facilitate treatment planning. The primary tumor (gross tumor volume; GTV primary) was delineated in the pulmonary windows, and the nodal involvement (GTV node) was delineated in the mediastinal windows. Clinical target volume (CTV) included GTV primary, GTV node, ipsilateral hilum, and elective mediastinum for which the lower border was 3.0 cm below the carina until 40 Gy. After 40 Gy, CTV included GTV primary and GTV node. The planning target volume (PTV) was the CTV plus a margin to ensure that the prescribed dose was actually delivered to the CTV. The prescribed dose was 60 Gy in 30 fractions. The heterogeneity correction was used and the dose was prescribed at an isocenter. PTV was encouraged to cover 90% isodose surface. Portal verification was done for all treatment fields. It was ensured that the normal lung volume receiving more than 20 Gy (V20) was equal to or under 35% of the total lung volume. The maximal dose to the spinal cord should not exceed 45 Gy at any level.

Chemotherapy

All patients received concurrent chemotherapy during the period that they had thoracic radiotherapy. The regimens consisted of a combination of a platinum-based agent with one or two other agents. The full-dose chemotherapy regimens used were as follows: MVP (mitomycin C at 8 mg/m^2 on day 1, vindesine at 3 mg/m^2 on days 1 and 8, and cisplatin [CDDP] at 80 mg/m^2 on day 1; two cycles were administered concurrently with split-course radiotherapy (60 Gy), including a 1-week interruption at 30 Gy, every 4 weeks, followed by two consolidation cycles every 4 weeks) and CDDP-VNR (vinorelbine at 20 mg/m^2 on days 1 and 8 and CDDP at 80 mg/m^2 on day 1; two cycles were administered concurrently with continuous radiotherapy (60 Gy), followed by two consolidation cycles every 4 weeks). The weekly regimens, with reduced drug doses, employed were as follows: CBDCA-paclitaxel (weekly carboplatin at a dose yielding an area under the plasma concentration time curve [AUC] = 2 mg/ml min and paclitaxel at 40 mg/m^2 administered concurrently with continuous radiotherapy (60 Gy) for 6 weeks, followed by CBDCA at a dose targeted to achieve an AUC = 5 mg/ml min on day 1 and paclitaxel at 200 mg/m^2 on day 1 every 3–4 weeks × two cycles); CBDCA-CPT 11 (weekly CBDCA at a dose yielding an AUC = 2 mg/ml·min and irinotecan [CPT 11] at 20 mg/m^2 administered concurrently with continuous radiotherapy (60 Gy) for 6 weeks, followed by a CBDCA dose targeted to achieve an AUC = 5 mg/ml·min on day 1 and CPT 11 at 50 mg/m^2 on days 1 and 8, every 3–4 weeks × two cycles). For patients with heart or renal complications, only the weekly reduced-dose regimens were adopted, while in those without serious underlying disease or complications, the chemotherapy regimen was selected according to the preference of the treating physician and the desire of the individual patient. All four regimens were used throughout the study period. Twenty-one patients were treated with a full-dose regimen (MVP, 11; CDDP+VNR, 10) and 38 were treated with a weekly regimen (CBDCA+paclitaxel 31; CBDCA+CPT 11, 7).

The overall survival (OS; defined as the time from the start of treatment to death) was assessed as the primary endpoint of efficacy. Secondary endpoints included the locoregional control (LRC) and distant metastasis-free survival (DMFS) rates. Locoregional control was defined as the absence of any recurrences involving the same lung or any regional lymph nodes. All other recurrences were considered as distant metastases. Response was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) system,[16] based on follow-up CT scans.

The safety of the regimens was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.

The Kaplan-Meier method was used for estimating survival. Differences in survival were tested using the log-rank test. A multivariate analysis to identify factors correlated with the OS was planned with a Cox proportional hazards model; P values of less than 0.05 were considered to be statistically significant. All statistical analyses were performed by the application of Dr. SPSS II for Windows (SPSS, Chicago, IL, USA).

Results

The baseline characteristics of the patients are summarized in Table 1. During thoracic radiotherapy, 86% completed two cycles of concurrent chemotherapy with a full-dose regimen, while 81% completed at least five cycles of a weekly regimen. After the thoracic radiotherapy, consolida-

Table 1. Patient characteristics

	Full-dose regimen ($n = 21$)		Weekly regimen ($n = 38$)		P value
Age (years)					
Median	60		63		
Range	52–73		44–75		
	No. of patients	%	No. of patients	%	
Gender					
Male	19	90	28	74	0.125
Female	2	10	10	26	
PS					
0	16	76	24	63	0.890
1	5	24	14	37	
Histology					
Sq. c. ca	6	29	13	34	0.657
Non-sq. c. ca	15	71	25	66	
Adeno ca	9		24		
Large cell ca	1		0		
NSCLC	5		1		
Stage					
IIIA	10	48	17	45	0.832
IIIB	11	52	21	55	
PET staging					
Done	14	67	20	53	0.296
Not done	7	33	18	47	

PS, performance status; sq. c. ca., squamous cell carcinoma; adeno ca, adenocarcinoma; large cell ca, large cell carcinoma; NSCLC, non-small cell lung cancer; PET, positron emission tomography

Table 2. Dose intensity of concurrent chemotherapy and duration of radiotherapy

Planned DI (mg/m^2 per week)		Actual DI (mg/m^2 per week)	Relative DI (%)	Duration of radiotherapy (days)	
Agent		Mean	Mean	Median	Mean
CDDP	20	17.0	85	54	51.6
Mitomycin C	2	1.70	85		
Vindesine	1.5	1.25	84		
CDDP	20	17.3	86	47	47.4
Vinorelbine	10	9.00	90		
CBDCA (AUC)	2	1.67	84	44	46.0
Paclitaxel	40	32.5	81		
CBDCA (AUC)	2	1.52	91	46	45.6
CPT 11	20	14.3	86		

DI, dose intensity; CDDP, cisplatin; CBDCA, carboplatin; AUC, area under the plasma concentration time curve (mg/ml·min); CPT 11, irinotecan

tion chemotherapy was administered to 52% of the patients with the full-dose regimens and to 55% of those with the weekly regimens. The planned and actual dose intensity of the concurrent chemotherapy and the duration of radiotherapy are summarized in Table 2. Overall, the relative dose intensity of the concurrent chemotherapy was comparable for each regimen. The overall response rates in the patients treated with the full-dose regimens and weekly regimens were 81% and 84%, respectively. The adverse events encountered during treatment are listed in Table 3. All but one patient were evaluated on CT at least 5 months after radiotherapy. The overall incidence rate of radiation pneumonitis grade 2 or more was 29%. There was one treatment-related death; one patient treated with a full-dose regimen died of pneumonitis 8 months after the initiation of treatment.

With a median follow-up time of 30 months, the median OS in the entire group was 27 months (95% confidence interval [95% CI], 20–34 months). The OS, LRC, and DMFS rates in the entire group of 59 patients at 2 years were 61%, 45%, and 37%, respectively. In the univariate analysis, treatment with a weekly regimen was associated with a better OS than that with a full-dose regimen (2-year OS rate, 75% for weekly regimens vs 41% for full-dose regimens; $P = 0.011$; Fig. 1). Other factors (stage, IIIA or IIIB; histology, squamous cell carcinoma or not; staging PET scan, done or not) were not associated with the OS. In the multivariate analysis, treatment with a weekly regimen was the only significant factor for better OS, with a hazard ratio of 0.358, (95% CI, 0.169–0.758; Table 4).

There were recurrences in 43 of the 59 patients. The patterns of failure were as follows: locoregional only; 15%

Table 3. Grade 3 and 4 toxicities

Toxicity	Full-dose regimen (n = 21)		Weekly regimen (n = 38)		P value
	Grade 3	Grade 4 (%)	Grade 3	Grade 4 (%)	(Grade 3 + grade 4)
Anemia	4	0	3	3	0.933
Leukopenia	43	43	68	11	0.523
Granulocytopenia	33	38	18	34	0.296
Thrombocytopenia	19	0	5	8	0.472
Nausea/vomiting	5	0	0	0	0.175
Esophagus	0	0	3	0	0.453
Neurologic	0	0	3	0	0.453
Lung	0	4[a]	0	0	0.175
Infection	0	0	0	3	0.453
Febrile neutropenia	14		5		0.233

[a] Grade 5 toxicity

Table 4. Univariate and multivariate analyses for overall survival (OS)

	Univariate			Multivariate	
	Median, months (95% CI)	2-Year OS rate	P value	Hazard ratio (95% CI)	P value
Factors	–				
Entire group	27 (20–34)	61%			
Chemotherapy					
Weekly	46 (22–70)	75%	0.011	0.358 (0.169–0.758)	0.007
Full-dose	18 (16–21)	41%			
Stage					
IIIA	Not mature	61%	0.138	1.523 (0.694–3.346)	0.294
IIIB	26 (16–36)	58%			
Histology					
Sq. c. ca	24 (24–25)	63%	0.348	1.236 (0.587–2.603)	0.578
Non-sq. c. ca	Not mature	58%			
PET staging					
Done	46 (19–73)	70%	0.052	0.472 (0.221–1.007)	0.052
Not done	22 (12–32)	48%			

CI, confidence interval; sq. c. ca., squamous cell carcinoma

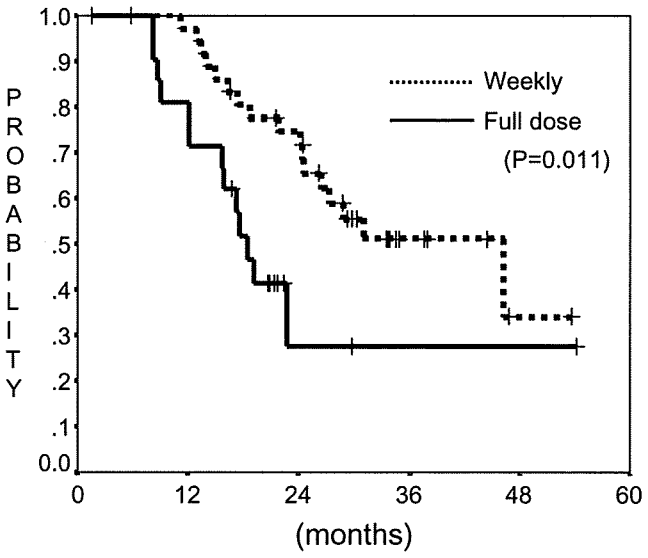

Fig. 1. Overall survival of the patients treated with the full-dose and weekly regimens

(2 of 13) and 27% (8 of 30), with the full-dose and weekly regimens, respectively; locoregional and metastases; 15% (2 of 13) and 13% (4 of 30), with the full-dose and weekly regimens, respectively; and metastases only; 69% (9 of 13) and 60% (18 of 30), with the full-dose and weekly regimens, respectively.

The brain was the first site of recurrence in 0% (0 of 13) and 23% (7 of 30) patients with the full-dose and weekly regimens, respectively. The chemotherapy regimen was not associated with the LRC (2-year LRC rate, 43% for weekly regimens vs 54% for full-dose regimens; P = 0.974) or the DMFS (2-year DMFS rate, 37% for weekly regimens vs 44% for full-dose regimens; P = 0.757).

Discussion

Overall, our data demonstrated encouraging survival in the entire subject group, and the OS in our study was better than that in two previously reported randomized trials.[6,17] Recently, the West Japan Thoracic Oncology Group presented the results of a phase III randomized trial (0105).[18]