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.

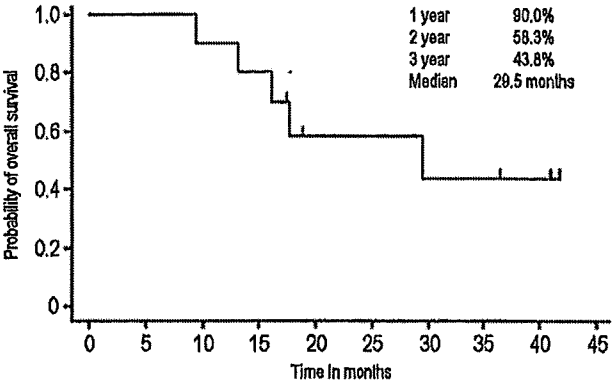

Fig. 2. Overall survival of patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent carboplatin/paclitaxel (CBDCA/PTX)

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

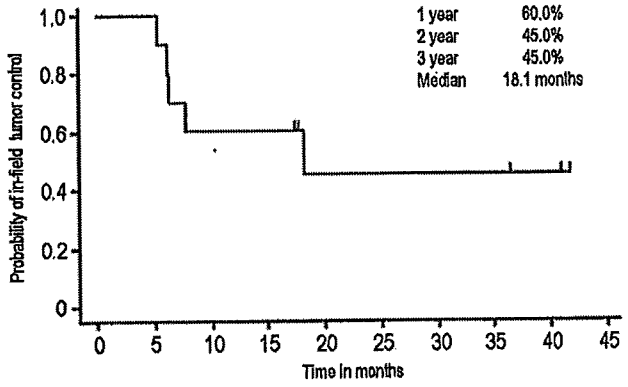

Fig. 3. In-field tumor control in patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent CBDCA/PTX

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

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)

(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] (2005)	PI	17	I–III	CBDCA PTX	CON (100%)		(V20 ≤ 30%)				
						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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Int J Clin Oncol (2009) 14:237–244
DOI 10.1007/s10147-008-0851-6

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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

Received: August 22, 2008 / Accepted: October 9, 2008

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

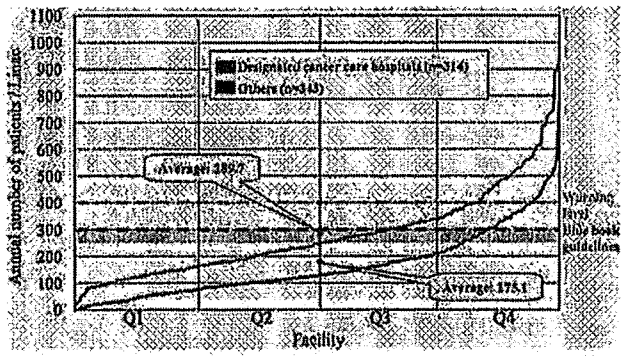


Fig. 1. Distribution of annual patient load/linear accelerator (*Linac*) in designated cancer care hospitals and the other radiotherapy (RT) facilities (*others*). *Horizontal axis* represents facilities arranged in order of increasing annual number of patients/Linac within facilities. The above-mentioned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

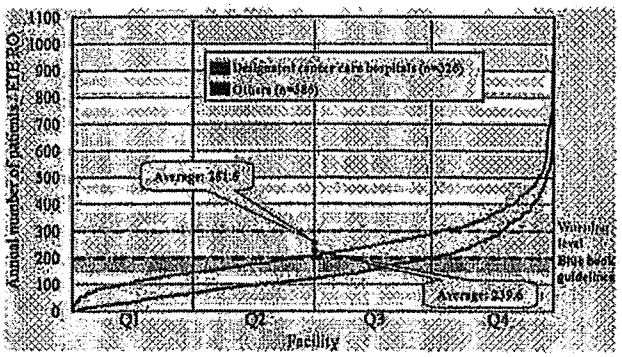


Fig. 2. Distribution of annual patient load/ full-time equivalent radiation oncologist (*FTE RO*) in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual numbers of patients / FTE RO within facilities. The number 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

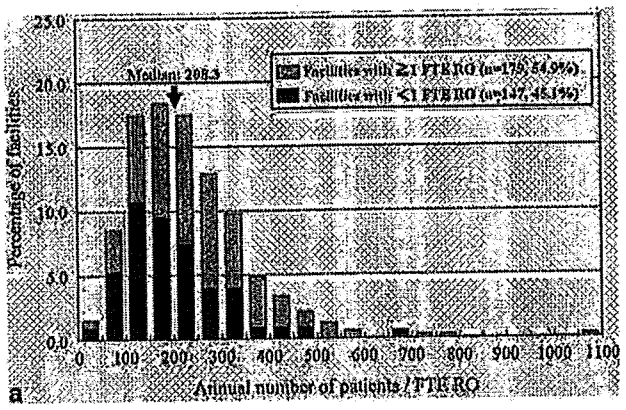
	Designated cancer care hospitals ($n = 326$)		Other RT facilities ($n = 386$)		*P*-value	Total ($n = 712$)	
	n	%	*n*	%		*n*	%
X-ray simulator	262	79.1[a]	240	61.7[a]	<0.0001	502	69.7[a]
CT simulator	217	63.5[a]	190	48.4[a]	<0.0001	407	55.3[a]
RTP computer (>= 2)	510 (101)	96.3[a] (38.5)	430 (45)	90.4[a] (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



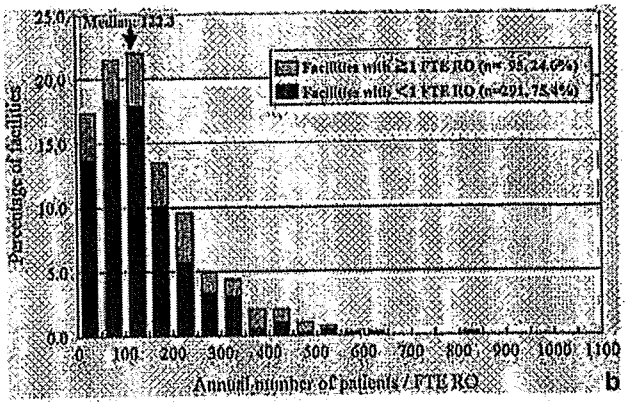


Fig. 3. **a** Percentage of facilities by patient load / FTE RO in designated cancer care hospitals. *Each bar* represents an interval of 50 patients per FTE RO. The number of FTE ROs for facilities with less than one FTE was calculated as FTE = 1 to avoid overestimating patient load / FTE RO. **b**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

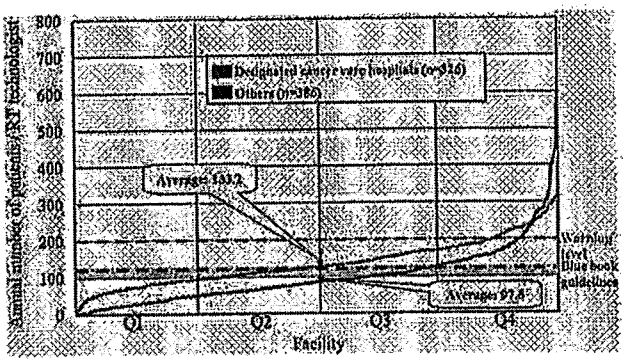


Fig. 4. Distribution of annual patient load / RT technologist in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual number of patients / RT technologist within facilities. *Q1-Q4*, As in Fig. 1 legend

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

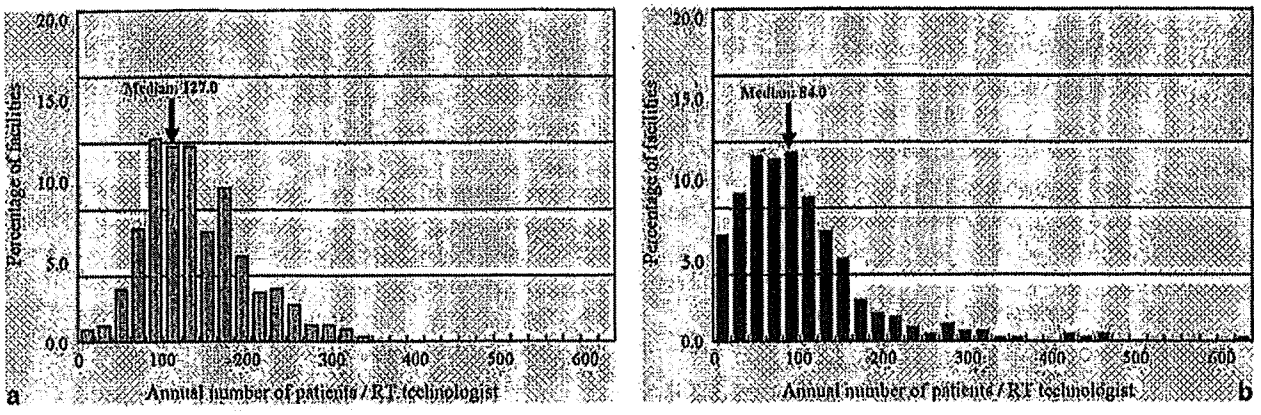


Fig. 5. a Percentage of facilities by patient load / RT technologist in designated cancer care hospitals. *Each bar* represents an interval of 20 patients per FTE staff. b Percentage of facilities by patient load / RT technologist in the other RT facilities. *Each bar* represents an interval of 20 patients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

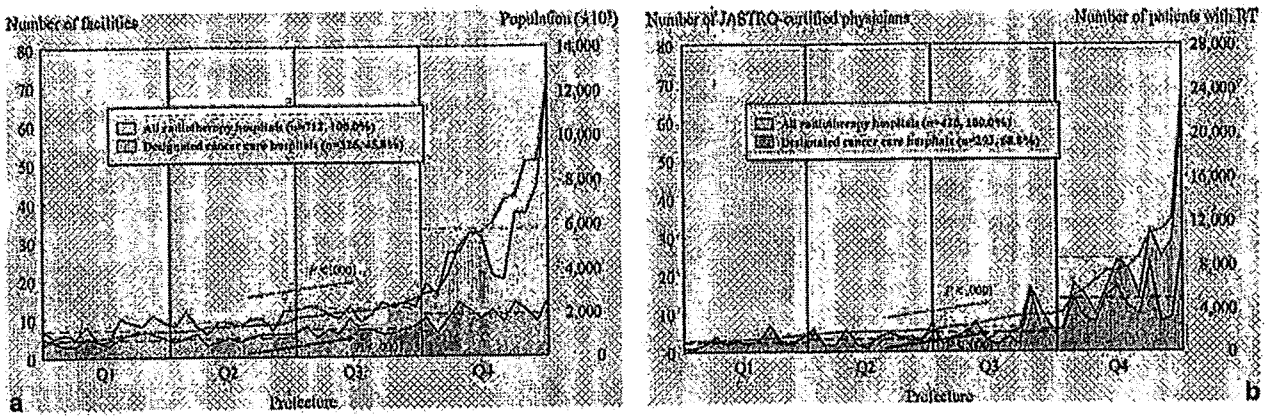


Fig. 6. a Geographic distribution, for 47 prefectures, of the number of facilities arranged in order of increasing population. *Upper dashed horizontal bar* shows average number of facilities in the prefectures per 4 separated groups (Q1–Q4) in all RT hospitals, and *lower dashed horizontal bar* shows 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.

Acknowledgments This study was supported by JASTRO. We wish to thank all ROs and radiation technologists throughout Japan who participated in this survey for their efforts in providing us with valuable information to make this study possible.

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Radiotherapy and Oncology 91 (2009) 433–437

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer RT

Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses

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ARTICLE INFO

Article history:
Received 3 October 2008
Received in revised form 29 December 2008
Accepted 30 December 2008
Available online 21 January 2009

Keywords:
Chemoradiotherapy
Elective nodal failure
Elective nodal irradiation
Non-small-cell lung carcinoma
Radiotherapy

ABSTRACT

Introduction: The role of elective nodal irradiation of non-small-cell lung cancer (NSCLC) patients treated with radiotherapy remains unclear. We investigated the significance of treating clinically uninvolved lymph nodes by retrospectively analyzing the relationship between loco-regional failure and the irradiated volume.

Methods: Between 1998 and 2003, patients with IA–IIIB NSCLC were treated with radiotherapy. The eligibility criteria for this study were an irradiation dose of 60 Gy or more and a clinical response better than stable disease. Typical radiotherapy consisted of 40 Gy/20 fr to the tumor volumes (clinical target volume of the primary tumor [CTVp], of the metastatic lymph nodes [CTVn], and of the subclinical nodal region [CTVs]), followed by off-cord boost to CTVp+n to a total dose 60–68 Gy/30–34 fr. The relationship between the sites of recurrence and irradiated volumes was analyzed.

Results: A total of 127 patients fulfilled the eligibility criteria. Their median overall and progression-free survival times were 23.5 (range, 4.2–109.7) and 9.0 months (2.2–109.7), respectively. At a median follow-up time of 50.5 months (range, 14.2–83.0) for the surviving patients, the first treatment failure was observed in 95 patients (loco-regional; 41, distant; 42, both; 12). Among the patients with loco-regional failure, in-field recurrence occurred in 38 patients, and four CTVs recurrences associated with CTVp+n failure were observed. No isolated recurrence in CTVs was observed.

Conclusions: In-field loco-regional failure, as well as distant metastasis, was a major type of failure, and there was no isolated elective nodal failure. Radiation volume adequacy did not seem to affect elective nodal failure.

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Radiation therapy is an integral component of the multi-modal treatment of non-small-cell lung cancer (NSCLC). Recent phase III studies have demonstrated that concomitant chemoradiotherapy improves survival, and this has resulted in the general acceptance of concurrent chemoradiotherapy as one of the standard treatments for locally advanced NSCLC [1]. Despite the improved survival, however, most patients die from their disease as a result of local or distant failure.

Local failure remains a major challenge when treating NSCLC with radiotherapy. A number of studies of dose escalation to the gross tumor volume (GTV) have been conducted as a means of improving local control [2–5]. The conventional radiation fields for NSCLC typically encompass the entire mediastinum and ipsilateral hilum (elective nodal region) to deliver a dose of 40 Gy, even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV. However, the conventional treatment has added considerable morbidity and can limit the dose escalation. In phase I–II dose escalation studies, there is a trend toward omitting the practice of elective nodal irradiation (ENI) after their experiences with toxicity, which is not based on direct evidence [2–5]. According to those studies, omitting ENI has not sacrificed treatment outcomes so far. They also analyzed patterns of recurrence in relation to irradiated volume in a dose escalation setting [6].

By contrast, the current literature provides limited information regarding patterns of failure when conventional fields and doses are used [7,8]. Since it is important to know whether loco-regional failure is within or outside the irradiation field, we retrospectively analyzed patterns of failure after radiation therapy for NSCLC, especially in regard to the relationship between local failure and irradiated volume.

Methods and materials

Patients

Between January 1998 and March 2003, 263 patients with newly diagnosed NSCLC were treated with thoracic radiation therapy,

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doi:10.1016/j.radonc.2008.12.013

with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

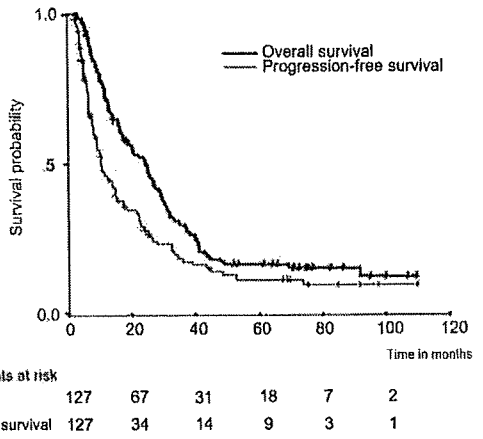

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Jpn J Clin Oncol 2009;39(11)707–712
doi:10.1093/jjco/hyp095

Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

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Received May 9, 2009; accepted July 8, 2009; published online August 19, 2009

Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

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with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in