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

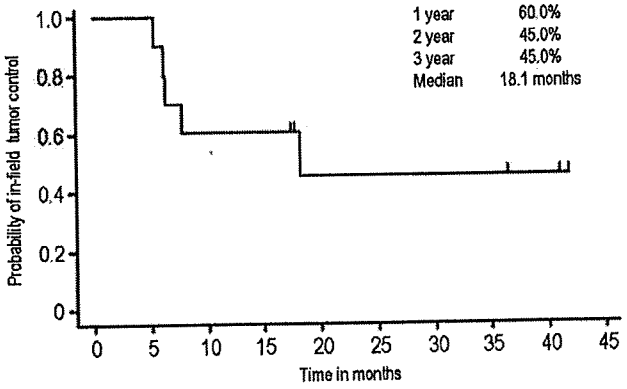

Fig. 3. In-field tumor control in patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent CBDCA/PTX

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 90.3	NR	0 0	0 9	7
							(25% ≤ V20 < 37%) 70.9 77.4	NR	0 0	0 8	
RTOG L-0117[22] (2005)	PI	17	I–III	CBDCA PTX	CON (100%)	2.15	(V20 ≤ 30%) 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	0
							74		0	17	
							78		0	50	
CALGB 30105[24] (2008)	PII	42	III	CBDCA PTX	CON (93%)	2 2	74 74[a]	37[b] 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

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

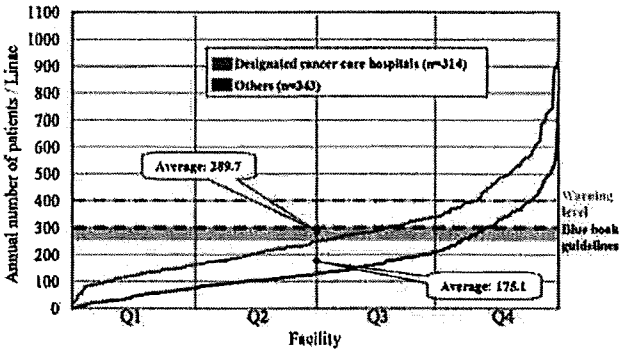

Fig. 1. Distribution of annual patient load/linear accelerator (*Linac*) in designated cancer care hospitals and the other radiotherapy (RT) facilities (*others*). *Horizontal axis* represents facilities arranged in order of increasing annual number of patients/Linac within facilities. The above-mentioned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

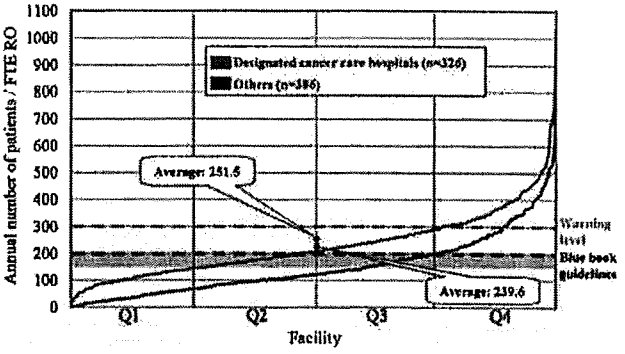

Fig. 2. Distribution of annual patient load/ full-time equivalent radiation oncologist (*FTE RO*) in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual numbers of patients / FTE RO within facilities. The number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

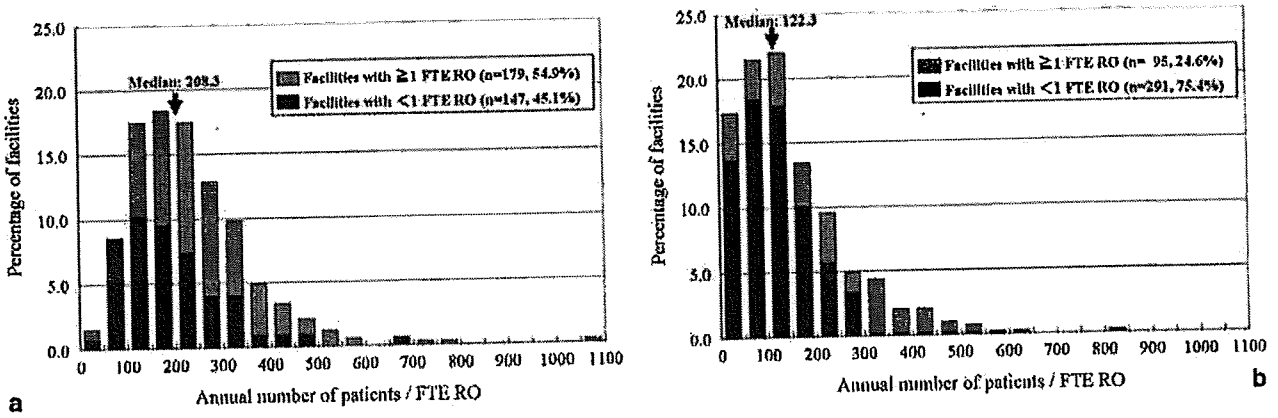

Fig. 3. **a** Percentage of facilities by patient load / FTE RO in designated cancer care hospitals. *Each bar* represents an interval of 50 patients per FTE RO. The number of FTE ROs for facilities with less than one FTE was calculated as FTE = 1 to avoid overestimating patient load / FTE RO. **b**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

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

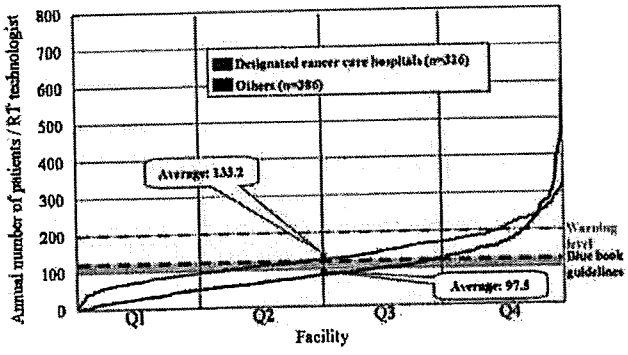

Fig. 4. Distribution of annual patient load / RT technologist in designated cancer care hospitals and the other RT facilities. *Horizontal axis* represents facilities arranged in order of increasing annual number of patients / RT technologist within facilities. *Q1-Q4*, As in Fig. 1 legend

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

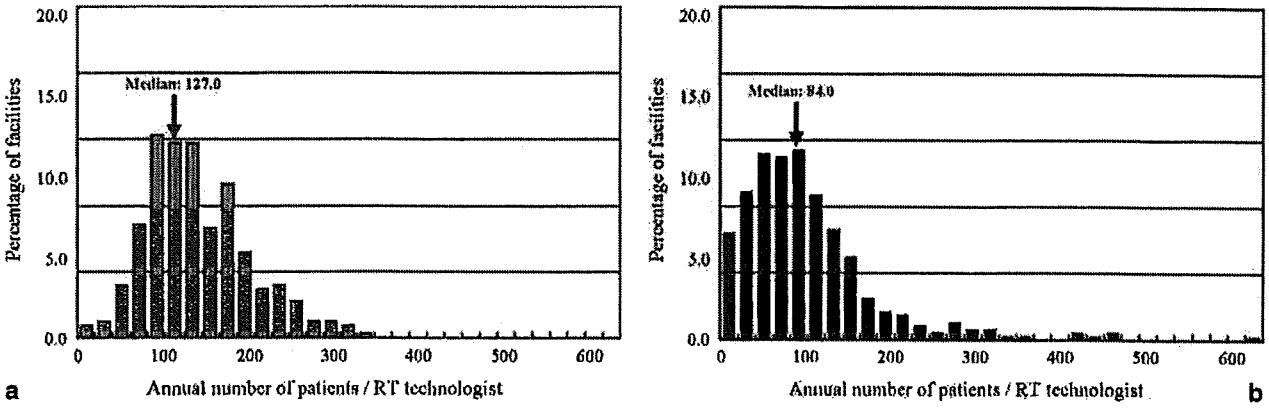

Fig. 5. **a** Percentage of facilities by patient load / RT technologist in designated cancer care hospitals. *Each bar* represents an interval of 20 patients per FTE staff. **b** Percentage of facilities by patient load / RT technologist in the other RT facilities. *Each bar* represents an interval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

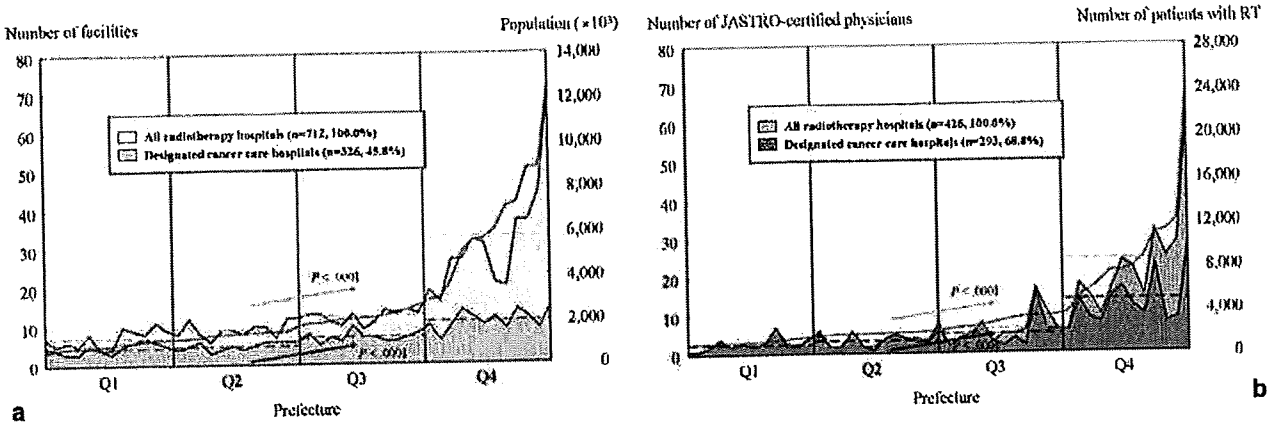

Fig. 6. **a** Geographic distribution, for 47 prefectures, of the number of facilities arranged in order of increasing population. *Upper dashed horizontal bar* shows average number of facilities in the prefectures per 4 separated groups (Q1–Q4) in all RT hospitals, and *lower dashed horizontal bar*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

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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Int J Clin Oncol (2008) 13:54–61
DOI 10.1007/s10147-007-0724-4

ORIGINAL ARTICLE

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Comparisons of the impact of systematic uncertainties in patient setup and prostate motion on doses to the target among different plans for definitive external-beam radiotherapy for prostate cancer

Received: May 25, 2007 / Accepted: September 11, 2007

Abstract
Background. We aimed to compare the impact of systematic uncertainties in patient setup and prostate motion on three different external-beam radiotherapy protocols for prostate cancer.
Methods. To simulate possible near-maximum systematic errors, the isocenter position was shifted to eight points with ±1.65 SD of the integrated uncertainty value along each axis that was expected to include 5%–95% of the total systematic uncertainties in each direction. Five cases were analyzed for the three plans: an old three-dimensional conformal radiotherapy (3D-CRT) protocol (four-field plus dynamic arc), a new 3D-CRT protocol (dynamic arc), and an intensity-modulated radiotherapy (IMRT) protocol, respectively.
Results. The averaged percentage volume covered by more than 95% of the prescription dose (V95) of the clinical target volume (CTV) for the original plans was 100% for all protocols. After simulating the errors, V95 of the CTV for IMRT cases was maintained at 100%. On the other hand, these values for the new and old 3D-CRT protocols were 93.1% and 63.2%, respectively. The values for the percentage prescription dose received by at least 95% volume (D95) of the CTV for the original plans were 100%, 98.4%, and 97.6% for the IMRT, new 3D-CRT, and old 3D-CRT plans, respectively. However, when the effects of the systematic errors were taken into consideration, the net decreases in the D95 values were 0.3%, 4.3%, and 8.1%, respectively.
Conclusion. The current IMRT protocol is considered to successfully compensate for systematic uncertainties. In contrast, the multi-leaf collimator (MLC) margins set for the old 3D-CRT protocol were not enough to ensure the actual delivery of the prescription dose to the CTV. Therefore, it is very important to include these issues in the plan design in the interpretation of clinical outcomes.

Key words Systematic uncertainties · Dynamic-arc 3D-CRT · IMRT · Prostate cancer

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Introduction

Geometrical uncertainties in radiotherapy can cause differences between the planned and the actually delivered dose distribution. The uncertainties mainly consist of setup deviation and internal organ motion. Both uncertainties can be separated into random and systematic components.

Setup error and organ motion in external-beam radiotherapy for prostate cancer have been widely investigated using megavoltage film or an electronic portal image device (EPID),[1–3] sequential computed tomography (CT) scans,[4–9] implanted radiopaque markers,[3,10–12] and a B-Mode Acquisition and Targeting System (BAT).[13,14] With better understanding of these uncertainties, the margin added to the clinical target volume (CTV) to create the planning target volume (PTV) is gradually reduced in conformation therapy to reduce the irradiated dose and volume to the organs at risk and to increase the dose to the CTV. However, a PTV margin that is too small will result in geometrical errors at some or even all treatment fractions. It has therefore become increasingly important to quantify and verify whether the applied margins can account for the uncertainties. Among the components of errors, random errors mainly result in blurring the dose distribution.[15,16] This blurring due to the random errors tends to have a relatively small impact on doses to the target and normal structures.[15] On the other hand, systematic errors have a much larger potential to cause significant underdosing or overdosing to both the target and normal structures.[8,15,17]

Therefore, the present study was designed to compare the effect of systematic components of setup errors and prostate motion on prostate dose coverage among three

Table 1. Summary of the three definitive radiotherapy protocols

Protocols	Fields	PTV margins (mm)	MLC and jaw margins (mm)	Setup	Dose (Gy)	Dose prescription
Old 3D-CRT	MLC- Shaped box	Not created	Superior: 12 Inferior: 12 Lateral: 7	Supine without fixation	46	Isocenter
	Dynamic arcs	Not created	Superior: 12 Inferior: 12 Lateral: 7		24	Isocenter
New 3D-CRT	Dynamic arcs	9 (6, Posterior)	Superior: 8 Inferior: 8 Lateral: 3	Supine without fixation	74	Isocenter
IMRT	215° 280° 0° 75° 145°	9 (6, Posterior)	Dynamic MLC, automatic defined: 7–9 mm	Prone with hip fixation	74	D95 of the PTV = 95% (>90%)

PTV, planning target volume; MLC, multi-leaf collimator

definitive external-beam radiotherapy plans for localized prostate cancer, and hence to verify whether the margins set for the three protocols could account for those uncertainties.

Patients, materials, and methods

Description of the three definitive radiotherapy protocols

Since 1998, three definitive radiotherapy protocols have been applied to the treatment of localized prostate cancer at our institute. They are the old three-dimensional conformal radiotherapy (3D-CRT), new 3D-CRT and intensity-modulated radiotherapy (IMRT) protocols, respectively. Details of each planning protocol have already been reported.[18] Briefly, in the old 3D-CRT protocol, a planning target volume (PTV) was not created. A multileaf collimator (MLC) with a leaf width of 1 cm was directly fitted to the clinical target volume (CTV), which is the prostate, with margins. Forty-six Gy in 23 fractions was given, using the four-field box technique with MLC conformation to the CTV, followed by an additional 24 Gy in 12 fractions with the dynamic-arc conformal technique. In the four-field irradiation, MLC or jaw edges were placed directly on the CTV with margins of 12 mm in superior/inferior directions and 7 mm in the remaining directions based on the beam's eye view of each field. If a part of the posterior rectal wall was included in the lateral opposing fields, the MLC positions were manually adjusted to completely shield the posterior wall from the irradiated area by the bilateral fields. In the dynamic-arc conformal radiotherapy, two lateral arcs with 100° of rotation (from 36° to 136°, and from 226° to 326°) were used with dynamic conformal fitting of MLCs to the CTV with a 7-mm margin. In the new 3D-CRT and IMRT protocols, PTV was created by adding a 9-mm margin to the CTV, except for the posterior rectal-prostate interface, where a 6-mm margin was applied. For the new 3D-CRT protocol, two lateral dynamic arcs with 100° of rotation (from 36° to 136° and from 226° to 326°) were used by dynamic conformal fitting of MLCs to the PTV, in which a 3-mm margin was generally placed from the edge of the PTV to the tips of the MLCs. With respect to the superior and inferior directions, jaws were fitted with an 8-mm margin to the PTV to ensure 95% dose at the edge of the PTV. For the IMRT protocol, inverse optimization was used to achieve the goal that the percentage prescription dose received by at least 95% volume (D95) of the PTV should generally exceed 95% (at least 90%). The old and new 3D-CRT techniques are performed with the patients in the supine position without any fixation, while IMRT is applied with the patients immobilized in the prone position, using thermoplastic shells fixed to a rigid pelvic board Hip Fix (MedTec, Inc, Orange City, IA, USA) extending from the mid-thigh to the upper third of the leg and with the feet being put on a cushion support. Details of the three protocols are summarized in Table 1.

Institutional measured uncertainties

From March 2001 to March 2002, a study was conducted to measure setup errors and prostate motion using serial computed tomography (CT) verification scans. Ten patients in the supine position, without fixation devices, and eight patients in the prone position, fixed with a set of thermoplastic shells, were enrolled in the study. Three CT verification scans were performed at 2-week intervals for the whole course of radiotherapy for each patient. CT scans were conducted with the same conditions as the simulation scans; that is, empty rectum and moderately dilated bladder (0.5–1.0 h after micturition). The three serial CT scan images were registered to the simulation CT scan images using the same Digital Imaging and Communications in Medicine (DICOM) coordinates. The prostate was contoured and the center was reconstructed. Four reference points on the pelvic bony structure (two on the innermost edge of the femoral head, one on the anterior-superior edge of the coccyx, and one on the posterior-superior edge of the pubic symphysis) were chosen to calculate the relative position of the prostate along three axial directions. Compared with the relative prostate position on the simulation CT images, the systematic and random prostate motions were calculated. The systematic displacement was taken to be the difference between the prostate position in the planning scan and the mean position as calculated from the three treatment scans, and the random displacements were calculated as the devia-

Table 2. Institutional data of systematic uncertainties and the integration used for simulations

	1 SD of systematic setup error	1 SD of systematic prostate motion	1 SD of integrated systematic error ($\Sigma\delta^2 = IM^2 + SM^2$)	Simulating value 1.65 SD (5%–95% CI)
	Prone Supine	Prone Supine	Prone Supine	Prone Supine
LR (mm)	1.6 3.0	0.8 0.9	1.8 3.1	3.0 5.1
AP (mm)	1.6 3.4	2.1 3.7	2.6 5.0	4.3 8.3
CC (mm)	3.1 3.2	3.1 1.7	4.4 3.6	7.3 5.9

LR, Left-right; AP, anterior-posterior; CC, cranial-caudal; δ, total margin; IM, internal margin; SM, setup margin; CI, confidence interval

tion of the prostate position in each treatment scan from the mean position. Thus, one systematic and three random displacements were calculated for each patient. Regarding the whole study cohort, the SD for the systematic error was assessed as the SD of the ten patients in the supine position or the eight patients in the prone position. The SD for the random error was taken as the SD of 30 random displacements in the supine position or 24 in the prone position for the ten or eight patients, respectively. The differences between simulation and treatment CT coordinate positions of the center of the four pelvic bony reference points along three axes were, accordingly, calculated as the axial setup errors; the SD values of systematic errors are displayed in Table 2.

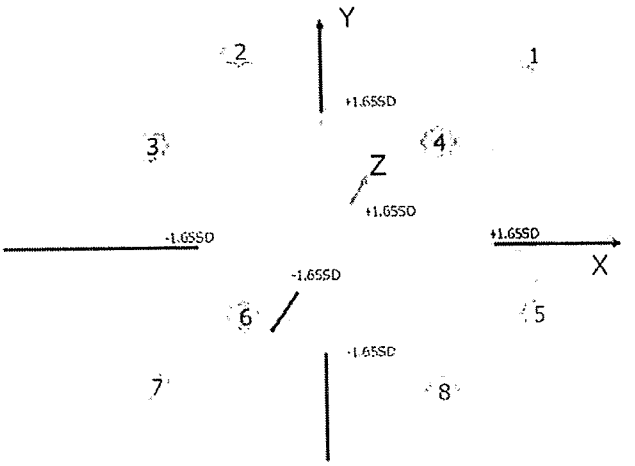

Fig. 1. Isocenter shifting model: ±1.65 SD was first chosen as the coordinate for axial check points (three pairs). Based on the six axial check points, eight vector combination points were created. The eight corner points were the worst-case scenario within a ±1.65 SD axial value

Isocenter shifting model simulating systematic setup errors and prostate motion

Integration of the systematic errors of the setup and internal prostate motion

The International Commission on Radiation Units and Measurements (ICRU) report 62 discussed several scenarios about how to composite the internal margin (IM) with the setup margin (SM). The report recommended creating a "global" safety margin to be adopted by means of the quadrature formalism ($\Sigma\delta 2 = IM2 + SM2$) in a quantitative approach.[19] According to the recommendation, we integrated setup errors and organ motions because the simple linear addition of two kinds of error would lead to an excessively large integrated systematic error. The calculated values of integrated systematic errors along the three axes are indicated in Table 2, for the supine and prone positions separately.

Representative shifting value of 1.65 SD along each of the three Cartesian directions

We assume that the prostate motions and setup errors can each be described by three orthogonal independent Gaussian (normal) distributions. This is a reasonable assumption, because several groups have proved that the data are normally distributed.[4,7,10,20] In this case, the calculated integrated systematic uncertainties should also be in normal distribution. Therefore, 90% (5% to 95%) of the systematic uncertainties are included within ±1.65 SD. This is because, if we consider a patient group as a whole, the mean value of the systematic errors would be very close to zero, as indicated in our institutional results. Therefore, in this study, we chose 1.65 SD of the integrated systematic uncertainties on each of the three axes, which was expected to cover 90% of the systematic isocenter shifts in each direction.

Simulating the impacts of the systematic errors on the dose distribution

To simulate the impacts of possible large systematic errors on the dose distribution, we shifted the isocenter to the eight points with +/−1.65 SD value on each axis (vector combination points; Fig. 1).

The isocenter shifting was conducted on five IMRT plans in the prone position with hip fixation, and on five new 3D-CRT plans in the supine position without fixation, and on

the old 3D-CRT plans created using the new 3D-CRT patients' contoured images strictly complying with the protocols. To further compare the new 3D-CRT protocol with the IMRT protocol, the five new 3D-CRT plans were created based on the respective CT data set for IMRT plans in the prone position with fixation devices complying with the planning protocol accordingly. The same magnitude of systematic uncertainties in the prone position with the fixation device was applied to simulate shifting the isocenter. All the created plans were checked and were approved by our department board. Shifted plans were created and dose distributions were recalculated. In total, 160 shifted plans were created and statistical data were collected and analyzed.

Analyses based on dose volume histogram (DVH) data

With the Eclipse treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA), the DVHs of the PTV and the CTV (prostate) were calculated for the original plans and the total shifted plan. The total shifted plan was defined as the plan with the averaged dose distribution of the eight shifted plans for each case. Therefore, the total shifted plan was considered to be the plan reflecting the averaged effect of the simulated systematic uncertainties. For the PTV and CTV, the percentage volume covered by more than 95% of the prescription dose (V95) and the percentage prescription dose received by at least 95% volume (D95) were calculated. In addition, minimal, maximal, and mean percent doses were collected for analyses. The dose conformity to the PTV was calculated using the conformity index (CI) equation advocated by Van't Riet et al.[21] The CI is defined as the product of the fraction of the PTV receiving at least 95% of the prescription dose and the ratio of the volume of the PTV receiving at least 95% of the prescription dose to the body volume receiving at least 95% of the prescription dose, which is indicated by the following equation:

$$\text{Conformity index (CI)} = \text{VPTV95\%/VPTV} * \text{VPTV95\%/Vt.}$$

Here, VPTV95% is the PTV volume covered by 95% of the prescription dose, VPTV is the volume of the PTV, and Vt is the body volume covered by 95% of the prescription dose. Therefore, the CI accounts for both any normal tissue volume receiving at least 95% of the prescription dose and for any volume of the PTV receiving less than 95% of the prescription dose. For the new and old 3D-CRT plans, because the same patients' images and systematic uncertainties for simulations of isocenter shifting were applied, comparisons of the DVHs for the same PTV and CTV were made. New 3D-CRT plans created on the CT data sets in the prone position were also compared to the corresponding IMRT plans with respect to the DVH indexes. The DVHs for the shifted plan for each case were calculated using a summed plan function with the same weight assigned to each single shift. The mean DVHs both for the original and shifted plans for each protocol were calculated by averaging their corresponding percentage volume at the same incremental dose steps. The P value was calculated by the two-tailed paired Student's t-test.

Results

Table 3 and Table 4 show the planning results of the PTV and CTV for five cases using the three respective protocols. The V95 and D95 values of the CTV for the three protocols were almost comparable ($P > 0.05$) and the differences in the other indexes among the three protocols were also small. However, when the same PTV definition as for the new 3D-CRT and IMRT protocols was applied to the old 3D-CRT protocol, the V95, D95, mean dose, and CI for the old 3D-CRT cases were greatly inferior to those for the cases with the other two protocols ($P < 0.001$), indicating

Table 4. RTP results for CTV with the three protocols

	IMRT (mean ± SD)	New 3D-CRT (mean ± SD)	Old 3D-CRT (mean ± SD)
V95 (%)	100 ± 0	100 ± 0	99.9 ± 0.1
D95 (%)	100 ± 0.9	98.4 ± 0.7	97.6 ± 0.6
Minimum dose (%)	98.1 ± 1.2	97 ± 0.6	95.3 ± 1.1
Maximum dose (%)	108.3 ± 1.8	102.6 ± 0.4	101.2 ± 0.5
Mean dose (%)	103.7 ± 0.7	100.7 ± 0.7	99.6 ± 0.3

V95, Percent target volume receiving 95% of the prescription dose or higher; D95, percent prescription dose covering 95% of the target volume

Table 3. RTP results for PTV with the three protocols

	IMRT (mean ± SD)	New 3D-CRT (mean ± SD)	Old 3D-CRT (mean ± SD)
V95 (%)	99 ± 0.5	93.9 ± 0.9	59.6 ± 6.8
D95 (%)	97 ± 0.5	94.5 ± 0.3	82.9 ± 1.5
Minimum dose (%)	87.7 ± 4.8	87.5 ± 0.7	60 ± 3.3
Maximum dose (%)	108.5 ± 1.8	102.6 ± 0.4	101.3 ± 0.5
Mean dose (%)	102.3 ± 0.7	99.5 ± 0.3	94.9 ± 1
Conformity index	0.88 (0.87–0.89)	0.76 (0.72–0.78)	0.60 (0.52–0.65)

V95, Percent target volume receiving 95% of the prescription dose or higher; D95, percent prescription dose covering 95% of the target volume; conformity index = $V_{PTV95\%}/V_{PTV}$* $V_{PTV95\%}/Vt$ [21]
For conformity index: mean (range)

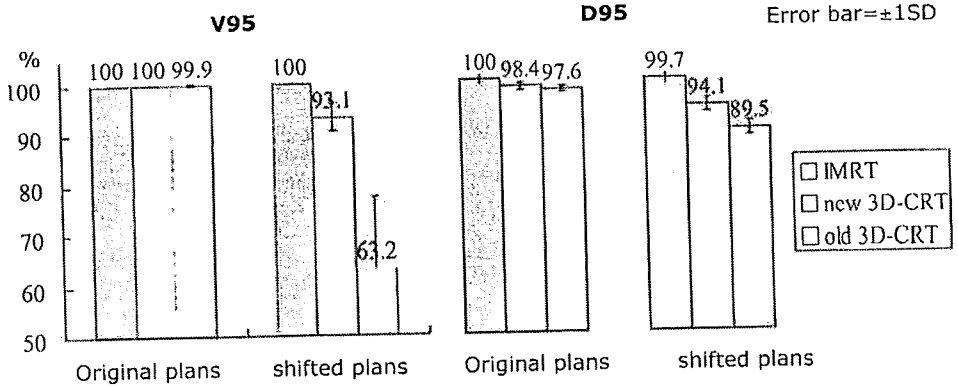

Fig. 2. Mean percent target volume receiving 95% of the prescription dose or higher (*V95*) and percent prescription dose covering 95% of the target volume (*D95*) for dose volume histogram (DVH) of the clinical target volume (CTV) of the three protocols before and after taking systematic uncertainties into consideration. *Error bar*, ±1 SD. *MRT*, modulated radiotherapy; *3D-CRT*, three-dimensional conformal radiotherapy

the original MLC margins set for this protocol are insufficient if the dose evaluation is based on the current PTV concept. The CI for the IMRT plans was the highest among the three protocols, which indicates the dose distributions in the IMRT plans conform best to the PTV compared to those in the new and old 3D-CRT plans.

Figure 2 indicates the V95 and D95 of the CTV for the original plans and the simulated isocenter-shifted plans. The V95s for all three protocols were excellent and reached 100% of the prescribed dose, while D95 values were also 97% or higher for all protocols. On the other hand, although the averaged V95 for total shifted IMRT plans was maintained at 100%, those for the new 3D-CRT and old 3D-CRT plans decreased to 93.1% and 63.2%, respectively. The decreasing rate of the V95 values for the old 3D-CRT cases was most evident compared with those for the other two protocol's cases. The same trend as for V95 was observed with respect to D95, although the magnitudes of the deterioration after simulating the systematic uncertainties in the old 3D-CRT cases were relatively smaller than those for the V95. The net decrease for IMRT cases was minimum (0.3%), while that for the old 3D-CRT cases was the biggest (8.1%) among the three protocols.

Figure 3 indicates the mean DVHs of the CTV for the original and total shifted plans of the three protocols. For the IMRT protocol, the two curves almost coincided with each other. Compared with the original new 3D-CRT plans, definitive insufficient dose coverage was observed with respect to the total shifted plans. Again here, the worsening of the CTV dose coverage for the old 3D-CRT plans was the most marked among the protocols. The detailed net decreases in the DVH statistics of the CTV after simulating the systematic uncertainties are indicated in Table 5.

The mean DVH of the CTV for the new 3D-CRT plans created on the CT data sets for the IMRT protocol is shown in Fig. 4. The net decreases in the V95, D95, minimum dose, maximum dose, and the mean dose for the IMRT protocol, the new 3D-CRT protocol, and the new 3D-CRT plans created on the CT data sets scanned in the prone position are indicated in Fig. 5. Although the net decreases in the V95, D95, minimum dose, maximum dose, and mean dose became much smaller when the new 3D-CRT plans were created with the patients in the prone position with hip fixation than when created with the patients in the supine

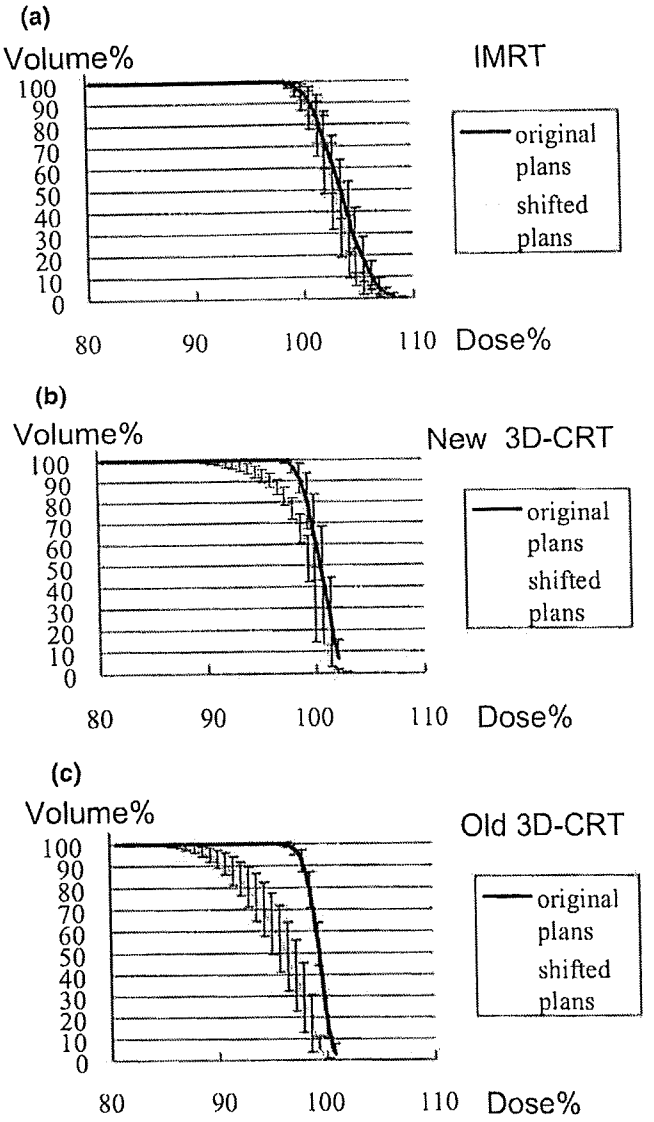

Fig. 3a–c. Mean DVH of the CTV before and after taking systematic uncertainties into consideration, for IMRT (**a**), new 3D-CRT (**b**), and old 3D-CRT protocols (**c**). *Error bar*, ±1 SD

Table 5. Comparison of the net decreases in the DVH statistics of the CTV for the three protocols after simulation of systematic uncertainties

	IMRT		New 3D-CRT		Old 3D-CRT	
	Net decrease (%)	*P* value	Net decrease (%)	*P* value	Net decrease (%)	*P* value
V95	0	0.4	6.9	0.005	36.7	0.004
D95	0.3	0.02	4.3	0.001	8.1	<0.0001
Min.	2.4	0.1	8.3	0.0001	11.8	<0.0001
Max.	1.7	0.003	1	0.006	1.3	0.003
Mean	0.7	<0.0001	1.5	0.0007	3.7	0.0008

V95, Percent target volume receiving 95% of the prescription dose or higher; D95, percent prescription dose covering 95% of the target volume

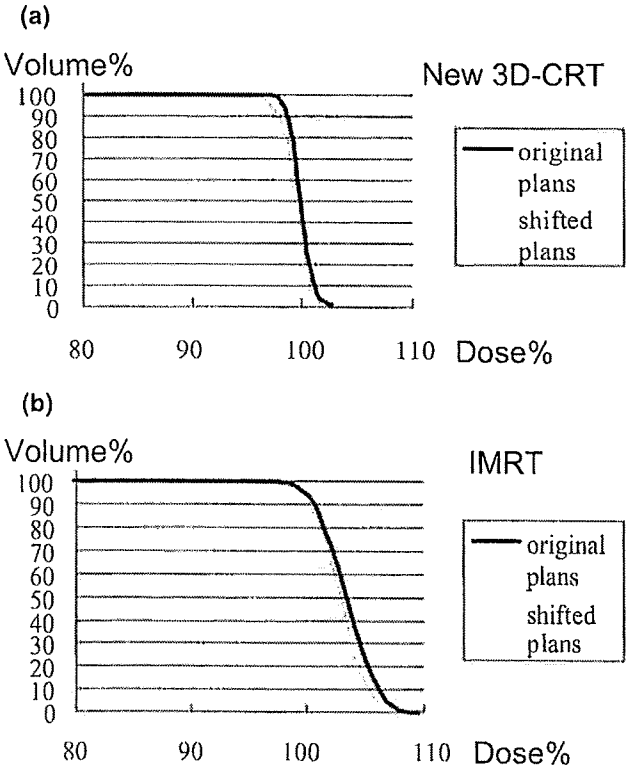

Fig. 4a,b. Comparison of the mean DVH of the CTV, for the new 3D-CRT (**a**) and IMRT plans (**b**) before and after taking systematic uncertainties into consideration based on the same condition: new 3D-CRT plans were created on the IMRT plan images and the systematic uncertainties of the prone position with hip fixation were simulated for the two protocol plans

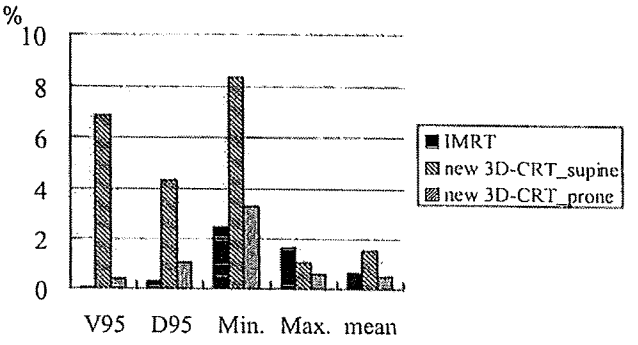

Fig. 5. Net decrease in the DVH indexes of the CTV for IMRT, new 3D-CRT_supine, and new 3D-CRT_prone plans after taking systematic uncertainties into consideration. *New 3D-CRT_supine* represents the new 3D-CRT plans simulating the systematic uncertainties in the supine position without using an immobilization device. *New 3D-CRT_prone* represents the new 3D-CRT plans created based on the IMRT plan images simulating the systematic uncertainties in the prone position with hip fixation

position without fixation, the IMRT plans still had some advantages in terms of target coverage.

Discussion

The ICRU report 50[22] recommends defining a geometrical structure of PTV to compensate for the effect of uncertainties. The magnitude of PTV can predict and project the potential location of the CTV. Margins to create the PTV from the CTV (PTV margin) should take into account both setup errors and internal organ motion. However, in most cases, the CTV is often located adjacent to the organs at risk (OARs), which prevents us from using margins large enough to cover all of the uncertainties for most patients. Therefore, adequate margins to compensate for 90%–95% of the uncertainties should be used to create the PTV. More importantly, the magnitude of the adequate margin is also influenced by the method of patient fixation or error reduction strategies. To see whether the defined margins account for the uncertainties, we examined and compared the adequacy of three definitive radiotherapy protocols for localized prostate cancer, in terms of the CTV coverage, by simulating possible large systematic errors with respect to patient setup and internal organ motion.

In the present study, several assumptions were made, based on the previously published literature; we assumed that random errors have a relatively smaller impact on the dose distribution to the prostate,[15-17] while systematic errors are in normal distribution.[4,7,10,20] Because our purpose was to compare planning strategies of three different radiotherapy protocols and to estimate their validity by verifying the tolerability in CTV coverage, we only simulated systematic

errors. To include all the possible systematic uncertainties, it would be necessary to apply nearly ±3 SD. However, we carefully chose ±1.65 SD of the systematic error as a checkpoint value for the isocenter shift, which includes 90% (from 5% to 95%) systematic uncertainties along each axis. Therefore, there were in total eight check points (Fig. 1). With these check points, we expected to include most of the possible systematic displacements while excluding very extreme shifts, which is reasonable for comparing the adequacy among different radiotherapy protocols.

Our previous study showed that the dynamic-arc 3D-CRT (new 3D-CRT) could achieve a comparable dose distribution to that achieved with IMRT with respect to the target coverage and rectal sparing in external-beam radiotheapy for localized prostate cancer with a prescription dose of 74 Gy. On the other hand, the old 3D-CRT plan could not reach a qualified dose coverage for the target, based on the current PTV concept, due to the universally smaller portal margins applied.[18] This continuing study shows that when the systematic uncertainties were incorporated into the dose distribution analyses, the difference between the planned and the actually delivered target dose was much larger for the old 3D-CRT plan, and a detectable dose decrease also appeared in the dynamic-arc 3D-CRT plan. However, the IMRT plan still maintained an intended target coverage of the prostate (CTV). Therefore the IMRT protocol is considered to be superior to the dynamic-arc 3D-CRT plan in terms of tolerability against systematic uncertainties.

A big question here is what are the adequate acceptance criteria with respect to the dose decrease from the planned to the actually delivered dose supposing the random factors could be neglected. The answer could not be drawn from the literature. van Herk[17] discussed this point in his review article and analyzed several examples, but the criteria were diverse and could not be uniformly applied: they should be institution-dependent and also treatment-technique-dependent. A general guideline for the target coverage in traditional static dose distribution is reported in ICRU report 50,[22] where the PTV should guarantee that 95% of the prescription dose is delivered to at least 90% of the CTV. Based on this guideline, the actually delivered dose distribution with the old 3D-CRT plans is unacceptable, which means margins applied directly to the CTV and simply defined by jaws/MLCs are universally insufficient to account for systematic uncertainties. However, the difference between the planned and actually delivered dose distribution to the CTV with IMRT plans is nominal, indicating that the margins set successfully compensate for the systematic uncertainties.

There are two main reasons why the ability to account for the systematic uncertainties between our IMRT and the new 3D-CRT protocol plans is different. One is patient position-related and immobilization-related uncertainty values, and the other is the treatment techniques themselves, which define dose conformity to, and the dose gradient from, the PTV. A comparison of the effect of the systematic uncertainties on the new 3D-CRT plans and the IMRT plans based on the same image pool simulating the same values of uncertainties, resulted in the slight superiority of the IMRT protocol to the new 3D-CRT protocol to account for the systematic uncertainties. At the same time, we also noticed that the degree of decrease in dose coverage after simulating the systematic uncertainties for the new 3D-CRT plans was much smaller when the patients were fixed in the prone position and immobilized with hip fixation than when they were treated in the supine position without any fixation devices. This may indicate that if, for our new 3D-CRT protocol, we also immobilize patients in the prone position with hip fixation, as is done with the patients receiving the IMRT protocol, we may get much better actual dose distribution. It has been reported that the prostate movement in the prone position was much larger that that in the supine position if no fixation devices were used, probably because of the effect of respiration.[11] Therefore, it is strongly recommended that we should use a fixation device when treating patients in the prone position.

There were some remarks in the literature that the IMRT was more sensitive to uncertainties than 3D-CRT due to its sharper dose gradients in the peripheral region of the PTV. Our data show that this is not necessarily true. The sensitivity to treatment-related uncertainties strongly depends on the given margins for the PTV and the error reduction strategies applied, as well as the degree of dose fall-off outside the PTV.

One drawback of the present study was that the effect of systematic uncertainties on the doses to the rectum and bladder was not incorporated into the dose distribution analyses of the target. The original planned dose range to the rectum and bladder was large, and rectum filling was diverse; all these factors make the incorporation much more complicated. Therefore, we believe a deformable image registration technique should be incorporated in the treatment planning based on a 4D imaging data set in the future.

In conclusion, differences in the CTV dose among three protocols for definitive external-beam radiotherapy when systematic uncertainties were taken into consideration were evaluated. Our current IMRT protocol, with fixation devices used in the prone position, was considered to successfully compensate for decreased systematic uncertainties, while the old 3D-CRT protocol was inadequate to realize an adequate CTV dose, although the CTV dose was sufficient in terms of the static protocol data. In the future, a 4D dataset-based method for radiotherapy protocol evaluation will be necessary to accurately estimate the actually delivered dose to the targets and organs at risk.

Acknowledgments This study was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas Cancer from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 17016036), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 16659316 and 17390333).

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