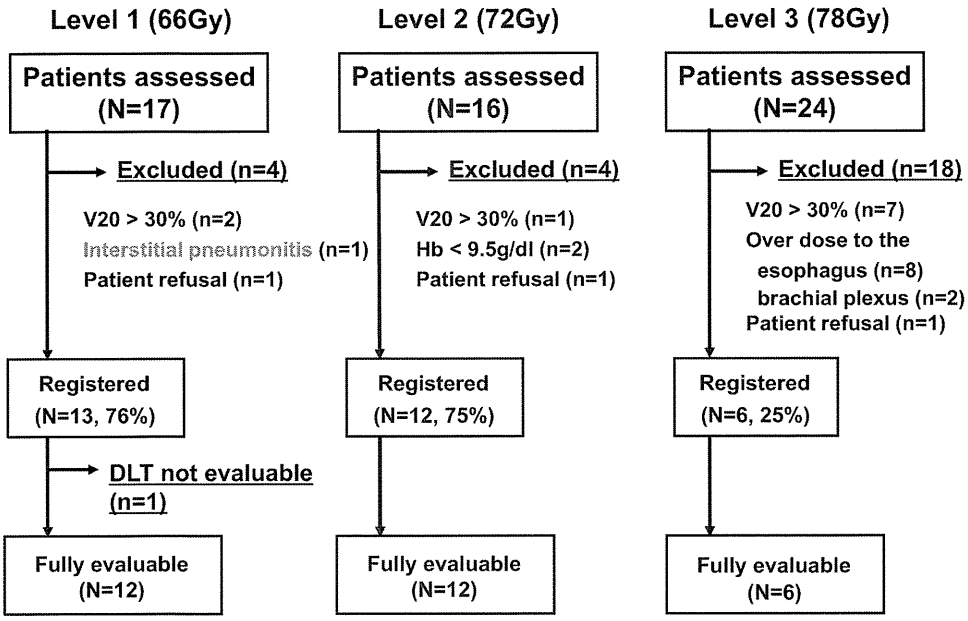

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (*n* = 13)	Level 2 (*n* = 12)	Level 3 (*n* = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

	Grade										
	Level 1			(n = 13)	Level 2			(n = 12)	Level 3			(n = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

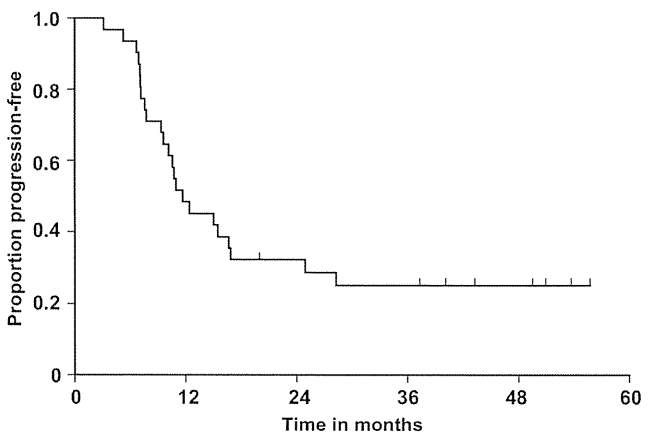

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (n = 31)

Sites	n	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

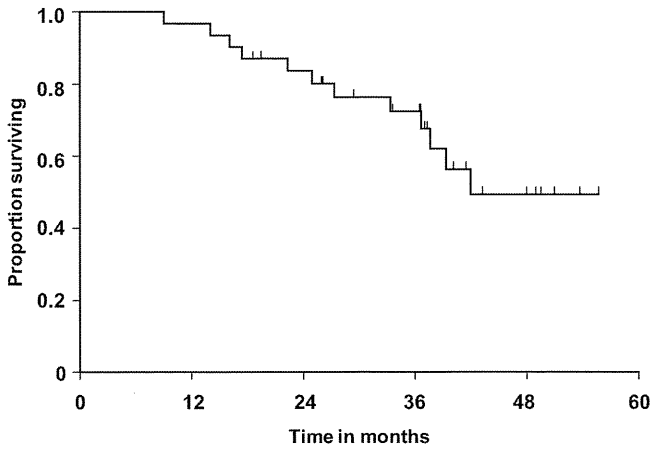

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

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CLINICAL INVESTIGATION **Brain**

COMPARISON OF CLINICAL OUTCOMES OF SURGERY FOLLOWED BY LOCAL BRAIN RADIOTHERAPY AND SURGERY FOLLOWED BY WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH SINGLE BRAIN METASTASIS: SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Purpose: Data comparing the clinical outcomes of local brain radiotherapy (LBRT) and whole brain RT (WBRT) in patients with a single brain metastasis after tumor removal are limited.

Patients and Methods: A retrospective analysis was performed to compare the patterns of treatment failure, cause of death, progression-free survival, median survival time, and Karnofsky performance status for long-term survivors among patients who underwent surgery followed by either LBRT or WBRT between 1990 and 2008 at the National Cancer Center Hospital.

Results: A total of 130 consecutive patients were identified. The median progression-free survival period among the patients who received postoperative LBRT ($n = 64$) and WBRT ($n = 66$) was 9.7 and 11.5 months, respectively ($p = .75$). The local recurrence rates (LBRT, 9.4% vs. WBRT, 12.1%) and intracranial new metastasis rate (LBRT, 42.2% vs. WBRT, 33.3%) were similar in each arm. The incidence of leptomeningeal metastasis was also equivalent (LBRT, 9.4% vs. WBRT, 10.6%). The median survival time for the LBRT and WBRT patients was 13.9 and 16.7 months, respectively ($p = .88$). A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the WBRT group ($p = .99$). The Karnofsky performance status at 2 years was comparable between the two groups.

Conclusions: The clinical outcomes of LBRT and WBRT were similar. A prospective evaluation is warranted.

Local brain radiotherapy, Whole brain radiotherapy, Single brain metastasis, Clinical outcomes, Long-term result.

INTRODUCTION

Whole brain radiotherapy (WBRT) has served as the standard of care for patients with brain metastases worldwide (1, 2). In patients with a single brain metastasis, postoperative WBRT has demonstrated better intracranial tumor control for both surgical lesions and nonsurgical new lesions and a lower rate of a neurologic cause of death compared with surgery alone (3). However, the addition of WBRT did not result in a survival benefit or extend the duration of the interval that the patients remained functionally independent. Some prospective trials, with the exception of one, and pooled analyses have clarified that a survival benefit for surgery followed by WBRT does exist compared with WBRT alone (1, 4–7). Other studies have also revealed that surgery followed by WBRT increased the duration of neurocognitive functional independence, as well as intracranial tumor control (4–6, 8, 9). Accordingly, surgery followed by WBRT has been the standard of care for patients with a single brain metastasis.

The median survival time of patients with brain metastases is considered to be approximately 2–7 months; favorable and unfavorable subgroups can be classified using recursive partitioning analysis (RPA) (10). However, about 2–8% of patients with brain metastasis can achieve longer survival periods (11, 12). Delayed WBRT toxicity, hypopituitarism, dementia, and memory disturbances influencing cognitive function have also been discussed, although the primary brain lesion is mainly responsible for the deterioration of functional independence (11, 13, 14).

Because WBRT is widely believed to induce dementia in patients with brain metastases, local brain RT (LBRT) as a substitute for WBRT has been widely accepted in some

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Table 1. Patient characteristics (n = 130)

Characteristic	All patients	Range	LBRT (n = 64)	WBRT (n = 66)	p
Age (y)	58	24–87	58 (38–87)	58 (24–79)	.35
Karnofsky performance status	70	40–100	70 (40–100)	70 (40–100)	.35
RPA class	II	I–III	II (I–III)	II (I–III)	.78*
I	40	30.8	19	21	
II	55	42.3	26	29	
III	35	26.9	19	16	
Cancer type (%)					.96*
Lung cancer	55	42.3	29	26	
Non–small-cell lung cancer	54		29	25	
Small-cell lung cancer	1		0	1	
Breast cancer	18	13.8	9	9	
Colorectal cancer	14	10.8	6	8	
Skin cancer	6	4.6	3	3	
Other	37	28.5	17	20	
Diameter of brain tumor (mm)	38	10–65	38 (10–65)	38 (15–60)	.57
Removal status					.11
Gross total removal	124	95.4	59	65	
Partial removal	6	4.6	5	1	

Abbreviations: RPA = recursive partitioning analysis; WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy,
Data presented as median, with range in parentheses.
* Chi-square test.

institutions in Japan (15). LBRT delivered by linear accelerator to the tumor bed with a margin determined using the two-field technique (opposing portal irradiation) according to a dose-fractionated schedule had been applied for the treatment of single brain metastasis after surgical removal at the National Cancer Center Hospital before September 2004. This was based on the ethics that we presumed we could treat intracranial relapse using stereotactic RT after LBRT. After discussion with neurosurgeons, radio-oncologists, and medical oncologists, however, the treatment policy was changed. WBRT has been used for the treatment of all patients with single brain metastasis after tumor removal since October 2004. A Phase I-II clinical trial of postoperative LBRT was reported, and the investigators concluded that LBRT was not a suitable substitute for WBRT (16). However, that previous study included only 12 patients, and 7 of these patients died of intracranial tumor progression. The median survival time was 7.2 months, similar to that after WBRT. Another retrospective study implied that LBRT might have a similar benefit to that of WBRT in patients with a single brain metastasis (17). Bahl *et al.* (18) reported 7 cases of postoperative LBRT, of which 4 cases recurred at the same site. These studies included only a small number of patients, and any conclusions regarding the clinical outcome of postoperative LBRT, especially compared with that of postoperative WBRT, are thus difficult to make. In the present analysis, we retrospectively compared the clinical outcomes of patients with a single brain metastasis who received surgery followed by either WBRT or LBRT.

PATIENTS AND METHODS

Patient population

From the database of the neurosurgery division at the National Cancer Center Hospital, we identified patients who had undergone brain tumor removal followed by RT between 1990 and 2008. The patients were included in the present analysis if they met the following criteria: age ≥18 years, a single brain metastasis identified by magnetic resonance imaging, and tumor removal followed by either WBRT or LBRT. The exclusion criteria were as follows: extracranial malignant lymphoma or hematological tumor; brain biopsy only; previous brain RT; surgery followed by observation, with brain RT once progression was recognized; and postoperative gamma knife or linear accelerator-based radiosurgery. All the patients who received LBRT (n = 64) were treated before October 2004, and all the patients who received WBRT (n = 66) were treated after October 2004.

Data collection and definitions of terms

All the medical charts for the eligible patients were reviewed. To compare the clinical outcomes of postoperative WBRT and LBRT, we collected the following data:; preoperative magnetic resonance imaging; date of surgery and RT; RPA classification before surgery; Karnofsky performance status (KPS) at presentation; primary tumor site; date of recognition of local recurrence or intracranial new metastases; patterns of progression; leptomeningeal metastasis development; date of death; and neurologic cause of death. For the additional evaluation of long-term survivors (≥2 years after surgery), we also reviewed the KPS at 2 years after surgery.

Local recurrence was defined as recurrence at the surgical site. Intracranial new metastases included the detection of new brain metastases other than those occurring at the surgical site or the development of leptomeningeal metastases. Leptomeningeal metastases were diagnosed using a cytologic examination of cerebrospinal fluid.

Surgery and RT

The surgical indications for single brain metastasis were generally as follows: tumor diameter ≥30 mm or a tumor diameter of <30 mm with neurologic dysfunction.

Whole brain RT was administered through two lateral ports covering the brain and meninges to the foramen magnum. Normally, WBRT was delivered using a 4-MV or 6-MV linear accelerator at

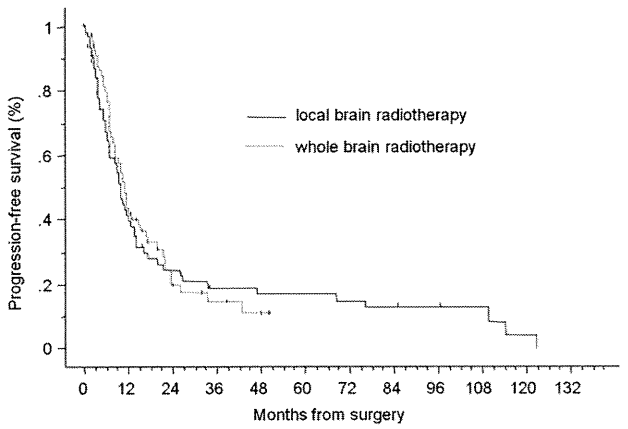

Fig. 1. Progression-free survival for patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

a total dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Patients who received LBRT underwent computed tomography simulation in the supine position. The clinical target volume consisted of the tumor cavity plus a 1.5-cm margin, and the planning target volume was created by expanding the clinical target volume by 0.5 cm. LBRT was administered using a 6-MV linear accelerator to the tumor bed using a two-field technique according to a dose-fractionated schedule. Normally, LBRT was delivered at a total dose of 50 Gy in 25 fractions.

Statistical analysis

Postoperative differences in local recurrence, intracranial new metastases, the development of leptomeningeal metastases, and neurologic cause of death were compared between the WBRT and LBRT groups using the Fisher exact test. Numeric data, including RPA, KPS, and age, were compared using the Mann-Whitney *U* test. Progression-free survival was defined as the interval between the date of surgery to the date of the recognition of local recurrence or intracranial new metastases. Death was treated as an event, and the absence of disease progression was treated as a censored observation on the last day of follow-up. Overall survival was defined as the interval from the date of surgery to the date of death. Patients who were lost to follow-up were treated as a censored observation on the last day of follow-up. Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify relevant factors affecting survival. The numeric factors analyzed in the Cox analyses were dichotomized according to the median number. All statistical analyses were performed using StatView, version 5.0 (SAS Institute, Tokyo, Japan).

RESULTS

Of the 421 surgical cases, we identified 130 patients who met the eligibility criteria. The characteristics of these patients are listed in Table 1. Of the 130 patients, 66 had received postoperative WBRT and 64 had received postoperative LBRT. Of the 66 patients who had received WBRT, 34 (51.5%) were treated to a dose of 30 Gy delivered in 10 fractions, and 31 (47.0%) were treated to a dose of 37.5 Gy delivered in 15 fractions. Of the 64 patients who received LBRT, 57 (89.1%) were treated to a dose of 50 Gy in 25 fractions, and 7 were treated with a variety of dose-fractionation schedules (24 Gy in 12 fractions to 60 Gy in 30 fractions).

The median progression-free survival period for the patients who received postoperative LBRT and WBRT was 9.7 and 11.5 months, respectively (p = .75; Fig. 1). The patients who underwent LBRT and WBRT developed 33 and 30 recurrences, respectively. The local recurrence rates (9.4% vs. 12.1%) and intracranial new metastases rates (42.2% vs. 33.3%) were not significantly different between the LBRT and WBRT groups (Table 2). The incidence of leptomeningeal metastases in patients receiving LBRT and WBRT was 9.4% and 10.6%, respectively (p = .99).

The median survival time for patients who received postoperative LBRT and WBRT was 13.9 and 16.7 months, respectively (p = .88; Fig. 2). Of the 64 patients who received LBRT and the 66 patients who received and WBRT, 59 and 49 died, respectively. A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the patients in the WBRT group (p = .99; Table 2). Univariate analyses revealed that only the RPA classification correlated significantly with survival (hazard ratio [HR], 0.436; p = .002). In particular, RT (LBRT vs. WBRT) did not correlate with survival (HR, 1.031; p = .88; Table 3). Multivariate analyses revealed that RPA was the only significant factor associated with survival (HR, 0.399; p = .001). Neither LBRT nor WBRT was related to survival (HR, 0.933; p = .74; Table 4).

Table 2. Patterns of treatment failure in patients who received WBRT and LBRT

Variable	LBRT (n = 64)	WBRT (n = 66)	
Total recurrences identified *(n)*	33	30	*p*
Local recurrence	6 (18.2)	8 (26.7)	.61
Distant metastasis	27 (81.8)	22 (73.3)	.61
Development of leptomeningeal metastases *(n)*	6	7	.99
Total deaths identified *(n)*	59	49	
Neurologic cause of death	21 (35.6)	18 (36.7)	.98*
Other	21 (35.6)	17 (34.7)	
Unknown	17 (28.8)	15 (30.6)	

Abbreviations: WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy.
Data in parentheses are percentages.
* Chi-square test.

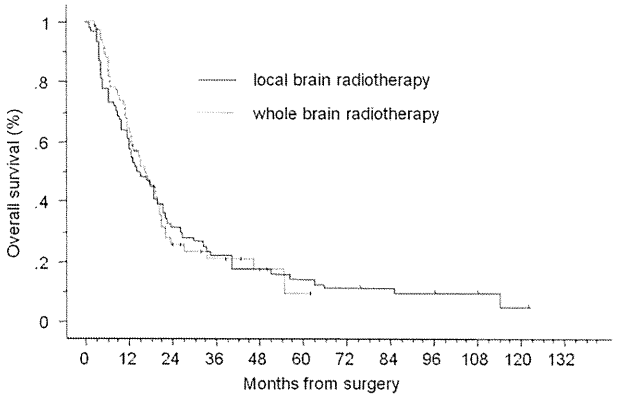

Fig. 2. Overall survival in patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

We further analyzed the patterns of RT after recurrence in patients who received either postoperative LBRT or WBRT. Of the 33 patients who developed recurrences after postoperative LBRT, additional RT was performed in 15 (45.5%). Of the 15 patients, 6 underwent gamma knife or linear accelerator-based radiosurgery. LBRT was performed in 5 patients, and 4 received WBRT. Of the 30 patients who developed recurrences after postoperative WBRT, 16 (53.3%) received additional RT. Of the 16 patients, 13 received gamma knife or linear accelerator-based radiosurgery, and 3 received LBRT.

Among the patients who survived for >2 years, we compared the KPS at 2 years after surgery. A total of 20 patients who had received postoperative LBRT and 13 who had received postoperative WBRT were identified. The median KPS score at 2 years for these patients in the LBRT and WBRT groups was 80 (range, 60–100) and 80 (range, 60–100; $p = .99$), respectively. Of the 20 patients who had received LBRT, 9 experienced relapse in a local lesion, 2 had focal signs without relapse, which might have indicated radiation necrosis, and 7 had been well without relapse. For 2 other patients, this information was not available.

DISCUSSION

We have revealed the clinical outcomes of postoperative LBRT among patients with single metastasis and compared them with those of patients who underwent postoperative WBRT. The clinical outcomes, including progression-free survival, overall survival, local recurrence, intracranial new metastases, development of leptomeningeal metastases, and neurologic cause of death, were not significantly different between the two groups. In an analysis of relapse patterns, the patients treated with LBRT tended to have a lower probability of developing local recurrence (9.4% vs. 12.1%) and a greater probability of developing intracranial new metastases (42.2% vs. 33.3%), although these values were not significantly different. The probability of developing leptomeningeal metastases was also similar in each group (9.4% vs. 10.6%).

Previous reports have indicated that the addition of WBRT after tumor removal significantly reduces the local recurrence rate (3, 9). However, approximately 6–50% of patients develop relapses at new intracranial sites in the brain (5, 9, 19). Furthermore, about 20–30% of patients with brain metastasis die of neurologic causes even if a radiation boost has been added using stereotactic radiosurgery to increase local control, although the presence of extracranial lesions is the strongest factor for predicting survival (7, 20, 21). In our study, intracranial new metastases were predominant in both groups. The frequency of intracranial recurrence (new local and intracranial metastases) was somewhat greater than in previous series, although the rate of a neurologic cause of death was equivalent. Importantly, the patterns of treatment failure were similar in the LBRT and WBRT groups. Muacevic *et al.* (22) insisted that postoperative WBRT should be applied in patients with a single brain metastasis to destroy so-called micrometastases, based on the results of their randomized trial. They compared patients with a small single metastasis who received either surgery plus WBRT or gamma knife surgery alone. Their sample size was underpowered, although the risk of intracranial new metastases seemed to be lower in the WBRT cohort. To date, no randomized trials comparing the clinical outcomes of postoperative WBRT and postoperative gamma knife or linear accelerator-based radiosurgery, or LBRT have been reported.

We have demonstrated a similar efficacy for LBRT and WBRT. WBRT has problems in terms of delayed toxicity developing leukoencephalopathy, although the number of long-term survivors with brain metastasis seems to be somewhat low (11, 12). LBRT might be beneficial with regard to the protection of normal brain tissue. We compared the KPS

Table 3. Univariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	1.031	0.698–1.523	.88
RPA classification			
I vs. III	0.436	0.259–0.733	.002
II vs. III	0.808	0.514–0.127	.35
Removal status (gross total removal vs. partial removal)	0.948	0.385–2.334	.91
Tumor diameter (≥38 vs. <38 mm)	1.053	0.718–1.543	.79
Cancer type (lung cancer vs. other)	0.694	0.470–1.025	.062

Abbreviations: RT = radiotherapy; HR = hazard ratio; CI = confidence interval; other abbreviations as in Table 1.

Table 4. Multivariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	0.933	0.614–1.416	.743
RPA classification			
I vs. III	0.399	0.232–0.688	.001
II vs. III	0.736	0.455–1.191	.22
Removal status (gross total removal vs. partial removal)	0.622	0.239–1.615	.33
Tumor diameter (≥38 vs. <38 mm)	0.852	0.559–1.297	.45
Cancer type (lung cancer vs. other)	0.662	0.438–1.001	.05

Abbreviations as in Tables 1 and 3.

at 2 years to examine any delayed toxicity. Because of the nature of the present retrospective study, the detailed neurocognitive function or quality of life of the patients could not be identified. Among the long-term survivors, however, the KPS was preserved in both treatment groups. Thus, LBRT might be indicated for elderly patients at risk of developing dementia if LBRT has the same ability to control primary brain tumors, which is considered to be the main factor affecting neurocognitive function (14).

The present study had some limitations because of its retrospective nature. First, the radiation dose varied. About 90% of the LBRT patients received a dose of 50 Gy delivered in 25 fractions, and approximately 50% of the WBRT patients received a dose of 30 Gy delivered in 10 fractions; the others received a dose of 37.5 Gy delivered in 15 fractions. According to the summary by Tsao *et al.* (1), no differences in terms of survival or neurocognitive function were observed among the various dose-fraction schedules of WBRT. Second, the present study was a historical case-control study comparing LBRT and WBRT. Patients at risk of developing multiple metastases might have undergone WBRT during the period before 2004, when we started performing WBRT as the standard of care. Thus, the patients who were treated with LBRT might have had better general condition compared with the patients who were treated with WBRT. We compared the baseline characteristics of each treatment arm and used multivariate analyses to reduce any potential biases.

CONCLUSIONS

We have demonstrated the clinical efficacy of LBRT compared with WBRT on a large scale. The clinical outcomes, including progression-free survival, overall survival, patterns of treatment failure, development of leptomeningeal metastases, and a neurologic cause of death, were similar in both treatment groups. The KPS at 2 years was also similar when the two groups were compared. This result should be evaluated in a prospective manner.

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CLINICAL INVESTIGATION **Prostate**

RADICAL EXTERNAL BEAM RADIOTHERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER IN JAPAN: CHANGING TRENDS IN THE PATTERNS OF CARE PROCESS SURVEY

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Purpose: To delineate changing trends in radical external beam radiotherapy (EBRT) for prostate cancer in Japan.
Methods and Materials: Data from 841 patients with clinically localized prostate cancer treated with EBRT in the Japanese Patterns of Care Study (PCS) from 1996 to 2005 were analyzed.
Results: Significant increases in the proportions of patients with stage T1 to T2 disease and decrease in prostate-specific antigen values were observed. Also, there were significant increases in the percentages of patients treated with radiotherapy by their own choice. Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing to 70 Gy from 2003 to 2005. Moreover, conformal therapy was more frequently used from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and from 1999 to 2001 (50.2%). On the other hand, the percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and from 1999 to 2001 (89.7%). Compared with the PCS in the United States, patient characteristics and patterns of treatments from 2003 to 2005 have become more similar to those in the United States than those from 1996 to 1998 and those from 1999 to 2001.
Conclusions: This study indicates a trend toward increasing numbers of patients with early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipment among Japanese prostate cancer patients treated with EBRT during 1996 to 2005 survey periods. Patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. © **2011 Elsevier Inc.**

Patterns of care study, Prostate cancer, Radical external beam radiotherapy, Changing trend.

INTRODUCTION

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish the national practice process of therapies for selected malignancies over a specific time period (1–3). In addition to documenting the practice process, data from PCS surveys are important for developing and disseminating national guidelines for cancer treatment that help promote a more uniform care process in the country. The PCS is also designed to complement the role of clinical trials in enhancing the standard of care for cancer patients (1, 4).

To improve the quality of radiation oncology, PCS methodology has been imported to Japan from the United States. The Japanese PCS Working Group of Prostate Cancer started a nationwide process survey of patients treated with radiotherapy between 1996 and 1998 (5, 6). Subsequently, the Working Group conducted a second PCS of patients treated with radiotherapy between 1999 and 2001 and previously reported the results of this second PCS for prostate cancer patients in Japan treated with radiotherapy (7–18). At present, we have conducted a third PCS of patients treated with radiotherapy from 2003 to 2005 (19).

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Conflict of interest: none.

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Over the past 10 years, remarkable changes have occurred in prostate cancer treatment policy in Japan. The number of deaths due to prostate cancer has been on a steep increase, especially in elderly patients. The proportion of prostate cancer deaths to total cancer deaths also showed an increase from 0.9% in 1960 to 4.2% in 2000 (20). Since the introduction of prostate-specific antigen (PSA) screening, prostate cancer cases are being detected at earlier stages of disease, which allows early-stage patients a better chance of successful treatment and reduction of death from prostate cancer (21, 22). Moreover, recently, the use of radical external beam radiotherapy (EBRT) for prostate cancer has increased rapidly, as significant new radiation treatment planning technologies and methodologies have become available. Therefore, to optimally treat Japanese prostate cancer patients, it is important to accurately delineate the intrinsic changes taking place in the national practice process of radiotherapy for prostate cancer in Japan. In this report, we present the results of our analysis of the time-dependent transition of the process of care for prostate cancer patients treated with radical EBRT in the time periods from 1996 to 1998, 1999 to 2001, and 2003 to 2005.

METHODS AND MATERIALS

PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 in Japan contain detailed information about a total of 1,286 patients with prostate cancer treated with radiotherapy during the respective survey periods (307 patients were treated in 1996-1998; 387 patients in 1999-2001 PCS; and 592 patients in 2003-2005). PCS methodology has been described previously (1–4). Briefly, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The Japanese PCS used an original data format developed in collaboration with the American College of Radiology (Philadelphia, PA). The PCS surveyors consisted of 20 radiation oncologists from academic institutions. For each institution, one radiation oncologist collected data by reviewing patients' charts. To validate the quality of the collected data, the PCS used an Internet mailing list including all of the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee.

Of the 1,286 patients comprising the PCS 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, patients with a diagnosis of adenocarcinoma of the prostate were eligible for inclusion in the present study unless they had one or more of the following conditions: (*1*) hormone-refractory cancer; (*2*) evidence of distant metastasis; (*3*) concurrent or prior diagnosis of any other malignancy; (*4*) prior radiotherapy; (*5*) or prior prostatectomy. In the current study, we considered the exclusion of patients with concurrent or prior diagnosis of nonmelanoma skin cancer would not affect the results of our PCS survey because the incidence of nonmelanoma skin cancers in Japan has been low compared to those in Western countries. A total of 841 patients with clinically localized prostate cancer treated with EBRT met these eligibility criteria and were selected for analysis (1996-1998 PCS included 161 patients from 51 institutions; 1999-2001 PCS included 283 patients from 66 institutions; and 2003-2005 PCS included 397 patients from 61 institutions). Criteria for institutional categories in the 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys have been detailed elsewhere (10, 11). Briefly, the PCS divided Japanese institutions into academic institutions (university hospital or cancer center) and nonacademic institutions (other hospitals).

In the current study, we used the risk groups utilized by D'Amico *et al.* (23), based on serum PSA level, biopsy, Gleason combined score, and 1992 American Joint Commission on Cancer (AJCC) clinical tumor category. Low-risk patients had a PSA of 10 μg/l or less, a Gleason score of 6 or less, and a 1992 tumor category of stage T1c or T2a. Intermediate-risk patients had PSA levels of 10.1 to 20 μg/l or a Gleason combined score of 7 or a 1992 AJCC tumor category of stage T2b. High-risk patients had a PSA level of more than 20 μg/l or a Gleason combined score of 8 or a 1992 AJCC tumor category of stage T2c.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University (24). Statistical significance was tested using the chi-square test, Student's *t* test, and the Mann-Whitney U test. A probability level of 0.05 was chosen for statistical significance.

RESULTS

Patient characteristics

Patient characteristics for the PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 are shown in Table 1. There were significant increases over time in the proportion of patients with stage T1 to T2 disease (34.6% of patients in the 1996-1998 PCS; 48.2% of patients in the1999-2001 PCS; and 61.4% of patients in the 2003-2005 PCS) and decreases in median PSA values at diagnosis (: 22.0 ng/ml in the 1996-1998 PCS; 20.0 ng/ml in the 1999-2001 PCS; and 14.9 ng/ml in the 2003-2005 PCS). Data for the Gleason combined score were missing for 73.9% (119/161) of the patients in the 1996 to 1998 PCS and for 39.6% (112/283) of the patients in the 1999 to 2001 PCS, while only 5.5% (22/397) of patients were missing in the 2003 to 2005 PCS. The number of patients in the low-risk group increased gradually over time, while the number of patients in the high-risk group decreased gradually (Fig. 1). Table 1 and Fig. 2 indicate the reasons for selecting radiotherapy during these different time periods. There were significant increases over time in the number of patients treated with radiotherapy by their own choice (5.9% of patients in the 1996-1998 PCS; 26.5% of patients in the 1999-2001 PCS; and 41.4% of patients in the 2003-2005). This change in the rate of "patient choice" was significantly different ($p < 0.0001$).

Treatment characteristics

Treatment characteristics are shown in Table 2. The frequencies of radiation energies >10 MV, the use of portal or electronic portal images, and all field treatment each day increased gradually from 1996 to 1998 to 2003 to 2005. Also, the frequency of computed tomography (CT)-based treatment planning was 90.9% in 2003 to 2005, but 80.7% in 1996 to 1998, and 85.5% in 1999 to 2001. Moreover, the frequency of conformal therapy increased more rapidly from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and 1999 to 2001 (50.2%).

Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Stratifying patients by

Table 1. Patient and disease characteristics

Patient characteristic	PCS survey 1996-1998 (n = 161 patients)	PCS survey 1999-2001 (n = 283 patients)	PCS survey 2003-2005 (n = 397 patients)	Significance (p value)
Institution	51	66	61	
Median age, years (range)	70.4 (46.5–89.8)	71.8 (49.7–92.2)	72.1 (50.7–87.7)	0.4556
Mean age ± SD	70.8 ± 8.1	71.8 ± 6.6	71.5 ± 6.1	0.3446
Median KPS % (range)	90 (40–100)	90 (50–100)	90 (60–100)	<0.0001
Mean ± SD	87.0 ± 8.9	89.1 ± 7.1	90.9 ± 8.5	<0.0001
Missing data	7	8	0	
Pretreatment PSA level (%)				
Median PSA level (range)	21.95 (0.3–900.0)	19.99 (0.6–856.9)	14.94 (0.7–3,058.0)	0.0176
Mean PSA level ± SD	51.5 ± 93.5	54.1 ± 99.5	48.2 ± 179.2	0.8719
<10	41/146 (28.1%)	77/268 (28.7%)	121/391 (30.9%)	0.0066
10-19.9	25/146 (17.1%)	57/268 (21.3%)	113/391 (28.9%)	
≥20	80/146 (54.8%)	134/268 (50.0%)	157/391 (40.2%)	
Missing data	15	15	6	
Lower pretreatment PSA level (%)				
<4	17/146 (11.6%)	8/268 (3.0%)	9/391 (2.3%)	<0.0001
≥4	129/146 (88.4%)	260/268 (97.0%)	382/391 (97.7%)	
Missing data	15	15	6	
Differentiation (no. patients/total) (%)				
Well	24/159 (15.1%)	62/264 (23.5%)	67/376 (17.8%)	0.0148
Moderate	79/159 (49.7%)	93/264 (35.2%)	152/376 (40.4%)	
Poor	46/159 (28.9%)	93/264 (35.2%)	99/376 (26.3%)	
Other	0/159 (0.0%)	2/264 (0.8%)	7/376 (1.9%)	
Unknown	10/159 (6.3%)	14/264 (5.3%)	51/376 (13.6%)	
Missing data	2	19	21	
Gleason combined score (%)				
2-6	11/42 (26.2%)	77/171 (45.0%)	118/375 (31.5%)	0.0014
7	18/42 (42.9%)	35/171 (20.5%)	134/375 (35.7%)	
8-10	13/42 (31.0%)	59/171 (34.5%)	123/375 (32.8%)	
Missing data	119	112	22	
T stage (no. patients/total) (%)				
TX-T0	1/159 (0.6%)	10/272 (3.7%)	1/394 (0.3%)	<0.0001
T1	8/159 (5.0%)	22/272 (8.1%)	88/394 (22.3%)	
T2	47/159 (29.6%)	109/272 (40.1%)	154/394 (39.1%)	
T3-T4	102/159 (64.2%)	124/272 (45.6%)	134/394 (34.0%)	
Unknown	1/159 (0.6%)	7/272 (2.6%)	17/394 (4.3%)	
Missing data	2	11	3	
N stage (no. patients/total) (%)				
NX-N0	136/157 (86.6%)	249/270 (92.2%)	372/394 (94.4%)	0.0038
N1	18/157 (11.5%)	15/270 (5.6%)	12/394 (3.0%)	
Unknown	3/157 (1.9%)	6/270 (2.2%)	10/394 (2.5%)	
Missing data	4	13	3	
Risk group (no. patients/total) (%)				
Low risk	1/127 (0.8%)	16/242 (6.6%)	40/381 (10.5%)	< 0.0001
Intermediate risk	7/127 (5.5%)	26/242 (10.7%)	107/381 (28.1%)	
High risk	119/127 (93.7%)	200/242 (82.6%)	234/381 (61.4%)	
Missing patient data	34	41	16	
Reason for selection of RT (no. patients/total) (%)				
Patient choice	8/136 (5.9%)	71/268 (26.5%)	159/384 (41.4%)	
Advanced or high-risk disease	43/136 (31.6%)	83/268 (31.0%)	121/384 (31.5%)	
Intercurrent disease	0/136 (0.0%)	0/268 (0.0%)	62/384 (16.1%)	
Medical contraindication	7/136 (5.1%)	36/268 (13.4%)	0/384 (0.0%)	
Old age	37/136 (27.2%)	44/268 (16.4%)	94/384 (24.5%)	
Other	9/136 (6.6%)	8/268 (3.0%)	6/384 (1.6%)	
NA or unknown	32/136 (23.5%)	26/268 (9.7%)	27/384 (7.0%)	
Missing data	25	15	13	

Abbreviations: KPS = karnofsky performance status; PSA = prostate-specific antigen; RT = radiotherapy; NA = data not available; SD = standard deviation.

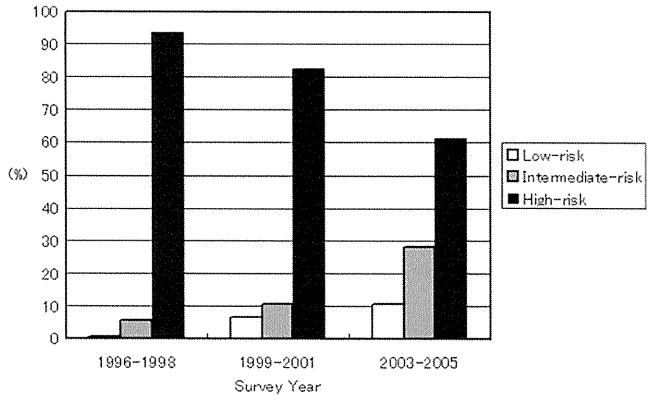

Fig. 1. Distribution of patients with prostate cancer according to risk group among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

total dosage revealed that 24.8% of patients received total radiation doses below 60 Gy in the 1996 to 1998 PCS, decreasing to only 2.0% from 2003 to 2005. Also, only 17.4% of patients received total doses of >70 Gy from 1996 to 1998, which increased dramatically to 52.0% from 2003 to 2005 (Fig. 3). Increased radiation doses were administered predominantly in academic institutions (Table 2).

The percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and that from 1999 to 2001 (89.7%). Hormonal therapy was used before, during, and after radiotherapy for a mean duration of 30.1 ± 29.8 months, 43.9 ± 36.7 months, and 40.6 ± 34.3 months, respectively (86.3% of patients in 1996-1998; 89.7% of patients in 1999-2001; and 81.1% in 2003-2005). The proportion of patients receiving hormone therapy was analyzed according to risk group. Most patients in the intermediate- and high-risk groups were treated with hormone therapy during 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods (Fig. 4). In the low risk-group, approximately 50% to 70% of patients were treated with hormone therapy in the periods 1999 to 2001 and 2003 to 2005. We could not precisely analyze the incidence of low-risk patients treated with hormone therapy during the 1996 to 1998 period because only 1 patient, who was not treated with hormone therapy, was available for this analysis.

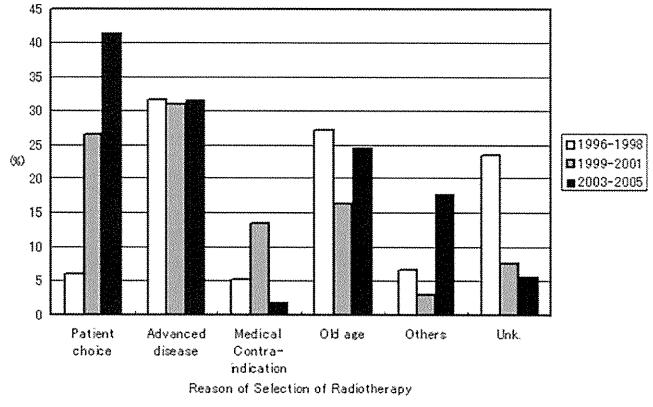

Fig. 2. Reasons of selection of EBRT for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

FTE radiation oncologists

For academic institutions, the mean numbers of full-time equivalent (FTE) radiation oncologists increased gradually over time (results of the surveys for 1996-1998, 1999-2001, and 2003-2005 were 2.13, 2.36, and 2.86, respectively). For nonacademic institutions, the mean numbers of FTE radiation oncologists also increased gradually over time (results for 1996-1998, 1999-2001, and 2003-2005 were 0.57, 0.62, and 0.75, respectively), but the numbers were extremely low compared with those in academic institutions.

Comparisons of changing trends in patient and treatment characteristics between Japan and the United States

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics by using the US PCS data reported by Zelefsky *et al.* (25). In Japan, the proportions of patients with stage T3 to T4 disease and PSA levels >20 ng/ml decreased gradually from 1996 to 1998 to 2003 to 2005, but the proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were over 30% among the three surveys (Fig. 5a). On the other hand, in the United States, the proportions of patients with T3 to T4 disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 disease, a PSA of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b).

Regarding treatment characteristics, in Japan, the proportions of patients receiving conformal radiotherapy and higher radiation doses (72 Gy or more) increased, as 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005. On the other hand, use of hormone therapy was over 80% during the survey periods (Fig.6a). In the United States, the proportions of patients receiving hormone therapy and higher radiation doses (72 Gy or more) increased continuously over the survey periods, and the proportions of patients receiving hormone therapy and higher radiation doses were approximately 45% to 50% (Fig. 6b). Concerning conformal therapy in the United States, 80% of patients were treated with conformal radiotherapy in 1999, which was almost the same frequency as patients treated from 2003 to 2005 in Japan.

DISCUSSION

Results of the current study indicate that there were significant increases in the proportions of prostate cancer patients with stage T1 to T2 disease and lower initial PSA values in the 1996 to 2005 survey periods in Japan. Numbers of patients in the low-risk group increased gradually, while

Table 2. Treatment characteristics

Treatment	PCS survey 1996-1998 (n = 161)	1999-2001 (n = 283)	2003-2005 (n = 397)	Significance (p value)
Received radiotherapy				
Energy (≥10 MV) (%)				
Yes (no. patients/total) (%)	98/161 (60.9%)	208/279 (74.6%)	312/386 (80.8%)	<0.0001
Missing data	0	4	11	
Portal films or electric portal images used (%)				
Yes (no. patients/total) (%)		210/280 (75.4%)	388/397 (97.7%)	<0.0001
Missing data		3	0	
All fields treated each day (%)				
Yes (no. patients/total) (%)	44/65 (67.7%)	215/283 (76.0%)	363/397 (91.4%)	<0.0001
Missing data	96	0	0	
CT-based treatment planning (%)				
Yes (no. patients/total) (%)	130/161 (80.7%)	241/282 (85.5%)	361/397 (90.9%)	0.0006
Missing	0	1	0	
Received conformal radiotherapy (%)				
Yes (no. patients/total) (%)	79/161 (49.1%)	142/283 (50.2%)	337/397 (84.9%)	<0.0001
Received pelvic irradiation (%)				
Yes (no. patients/total) (%)	69/161 (42.9%)	102/283 (36.0%)	95/397 (23.9%)	<0.0001
Radiation dose (cGy)				
A+B (total)				
Median (range)	6,500 (2,200–7,400)	6,840 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,090.9 ± 990.5	6,602.9 ± 731.1	6,764.0 ± 621.9	<0.0001
A median (min-max)	6,500 (2,200–7,400)	6,600 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,250.9 ± 976.8	6,610.3 ± 766.5	6,855.8 ± 708.0	<0.0001
B median (min-max)	5,940 (3,400–7,000)	6,900 (3,000–8,000)	6,600 (3,000–7,640)	<0.0001
Mean ± SD	5,622.4 ± 885.6	6,592.6 ± 681.9	6,654.9 ± 480.5	<0.0001
Prescription dose levels (Gy) (no. patients/total) (%)				
<60	40/161 (24.8%)	17/282 (6.0%)	8/396 (2.0%)	<0.0001
60-65	36/161 (22.4%)	56/282 (19.9%)	57/396 (14.4%)	
65-70	57/161 (35.4%)	102/282 (36.2%)	125/396 (31.6%)	
≥70	28/161 (17.4%)	107/282 (37.9%)	206/396 (52.0%)	
Missing data	0	1	1	
Higher prescription dose levels (no. patients/total) (%)				
<72	159/161 (98.8%)	261/282 (92.6%)	329/396 (83.1%)	<0.0001
≥72	2/161 (1.2%)	21/282 (7.4%)	67/396 (16.9%)	
Missing data	0	1	1	
Received hormone therapy (%)				
Yes (no. patients/total) (%)	138/160 (86.3%)	253/282 (89.7%)	321/396 (81.1%)	0.0284
No (no. patients/total) (%)	21/160 (13.1%)	29/282 (10.3%)	73/396 (18.4%)	
Unknown	1/160 (0.6%)	0/282 (0.0%)	2/396 (0.5%)	
Missing data	1	1	1	
Received chemotherapy				
Yes (no. patients/total) (%)	20/159 (12.6%)	17/274 (6.2%)	5/394 (1.3%)	<0.0001
No (no. patients/total) (%)	137/159 (86.2%)	255/274 (93.1%)	387/394 (98.2%)	
Unknown	2/159 (1.3%)	2/274 (0.7%)	2/394 (0.5%)	
Missing data	2	9	3	

Abbreviation: SD = standard deviation.

numbers of patients in the high-risk group decreased gradually. These results suggest that the likelihood of early-stage prostate cancer patients being treated with radiotherapy is greater than ever before in Japan. In the United States, most of the prostate cancer patients have early-stage tumors, and radiotherapy has been recognized as the first-line therapy for prostate cancer (25–28). Because of the prevailing use of PSA screening and the increasing number of patients treated with radiotherapy in Japanese institutions (29), the opportunities for treating early-stage prostate cancer patients with radical EBRT should increase even more in the future.

In the current study, the data for a Gleason combined score were missing for 73.9% of the patients in the 1996 to 1998 PCS and 39.6% of the patients in the 1999 to 2001 PCS, while data for only 5.5% of the patients in 2003 to 2005 PCS were missing. These results suggest that previously in Japan, physicians did not realize the importance of the

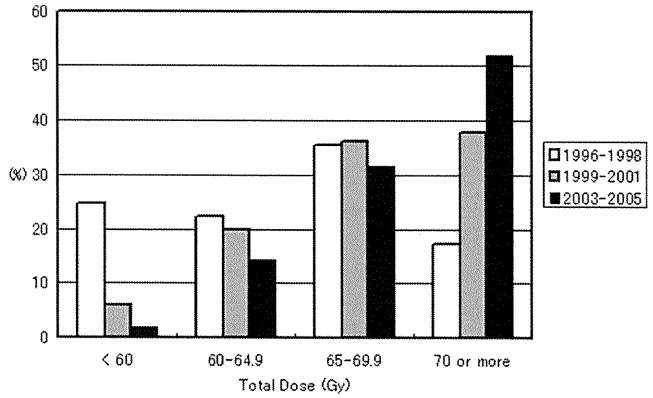

Fig. 3. Distributions of total radiation doses of external beam radiotherapy for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

Gleason combined score, but recently, they are becoming aware that the Gleason combined score is of critical importance in the evaluation and management of prostate cancer patients. Further studies are required to confirm whether physicians in Japan will routinely use the Gleason combined score in the management of prostate cancer patients in future.

The current study also revealed a remarkable change in the reason for choosing radiotherapy in Japan among the 1996 to 2005 survey periods. Only 5.9% of the patients were treated with radiotherapy by their own choice from 1996 to 1998, but 41.4% of patients chose radiotherapy from 2003 to 2005. EBRT did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an insufficient number of radiation oncology centers capable of delivering appropriate treatment prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technologies and methodologies for treatment planning and delivery, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (30, 31). Therefore, the increasing percentage of patients choosing radiotherapy might reflect a growing acceptance of radical external EBRT as one of the main treatments for prostate cancer patients in Japan.

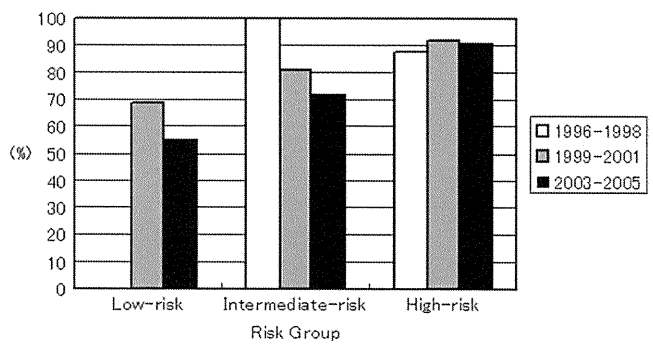

Fig. 4. Hormonal therapy distribution according to risk group for prostate cancer in Japan among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

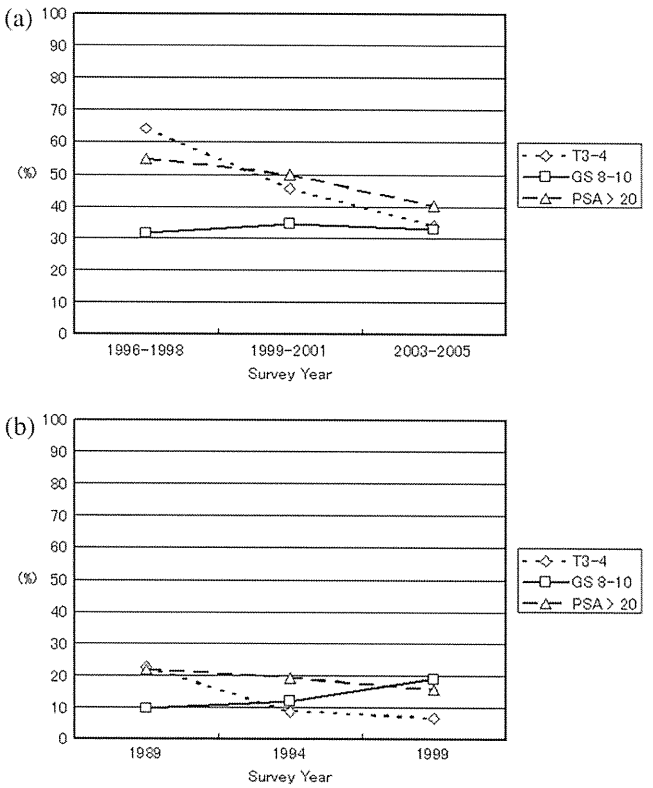

Fig. 5. (a) Changing trend in patient characteristics in Japan. (b) Changing trend in patient characteristic in the United States. (Data from ZelefskyMJ, Moughan J, Owen J, et al. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns of care survey for prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:1053-1061)

Moreover, the radiotherapy strategy appears to have changed among the 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods. The frequency of CT-based treatment planning increased up to 90.9% in 2003 to 2005, and the usage of conformal therapy increased rapidly from 2003 to 2005 (84.9%). The median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Also, the proportions of patients receiving total radiation doses below 60 Gy decreased, while the proportions of patients receiving total doses of >70 Gy increased rapidly during the survey period (Fig. 3). These results indicate that patients receiving lower radiation doses with obsolete treatment equipment was more common between 1996 and 1998, while higher doses with high-technology radiation equipment prevailed between 2003 and 2005. US PCS results indicate that many prostate cancer patients have been routinely treated with total doses of >70 Gy in the United States (25, 28). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (32–35) and also a growing acceptance by radiation oncologists and urologists that radical EBRT is effective for treating prostate cancer (30, 31).

Results of the current study indicate that hormone therapy was commonly used in conjunction with radiotherapy during the survey period in Japan. Moreover, it was not only

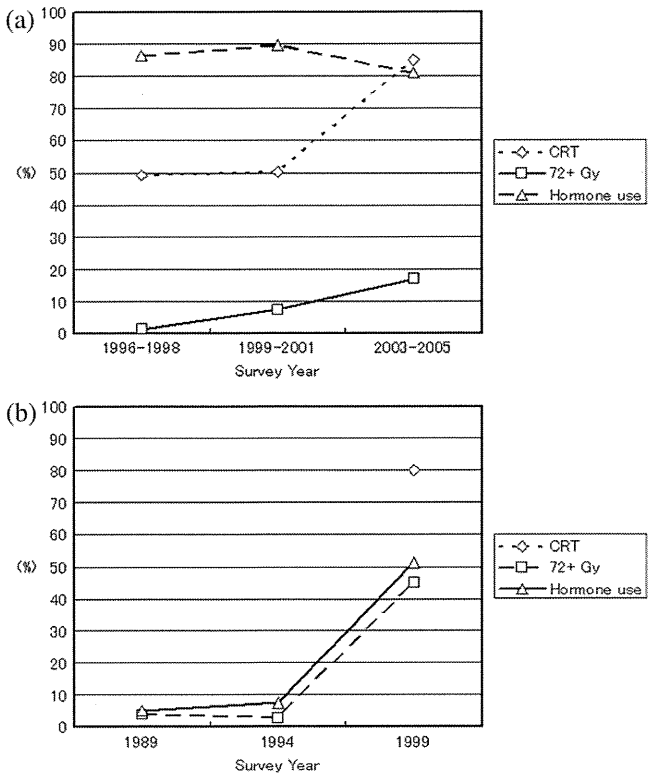

Fig. 6. (a) Changing trend in treatment characteristics in Japan. (b) Changing trend in patient characteristics in the United States. (*Data from* Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.)

patients in the intermediate- and high-risk groups but also patients in the low-risk group who were frequently treated with hormone therapy during 1999 to 2001 and 2003 to 2005 (Fig. 4). However, several studies from the United States have indicated that radical radiotherapy alone could control the disease in low-risk patients. Zietman *et al.* (34) indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was less than 10 ng/ml. Hanks *et al.* (35) found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose escalation above 70 Gy (35). Therefore, radical EBRT without hormone therapy has been the primary treatment for patients in the United States with low-risk diseases. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormone therapy in Japan (36). Another reason may be that at present, many Japanese radiation oncologists may consider the higher dose levels (>72 Gy) unnecessary for prostate cancer patients when combined with long-term hormone therapy. Therefore, radical EBRT without hormone therapy should also be the treatment of choice for low-risk patients in Japan.

In the current study, the mean numbers of FTE radiation oncologists increased gradually over time in both academic and nonacademic institutions. However, the median number of FTE radiation oncologists remained low, especially in nonacademic institutions. Publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy in every institution, demonstrating a need for both academic and nonacademic Japanese institutions to upgrade their radiation equipment and to recruit more radiation oncologists (29).

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics. In Japan, proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were all over 30%, but proportions of patients with T3 to T4 disease and a PSA level of >20 ng/ml decreased gradually during the survey period (Fig. 5a). In the United States, the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b). These results indicate that although patients in Japan had more advanced disease than those in the United States, patient characteristics in Japan have been changing, becoming more similar to patients in the United States. Further studies are required to confirm this finding.

Concerning treatment characteristics: in Japan, proportions of patients receiving conformal radiotherapy and higher radiation doses have been increasing, and 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005 (Fig. 6a). In the United States, conformal therapy was administered to 85% of patients in 1999, and higher radiation doses (72 Gy or more) have increased continuously from 1989 to 1999 (Fig. 6b). These results indicate that although radiotherapy characteristics were still developing in Japan compared to the United States, the proportions of modern radiotherapy have been increasing both in Japan and the United States during the survey period.

The percentage of patients receiving hormone therapy remained high during the periods from 1996 to 1998 to 2003 to 2005 in Japan. On the other hand, there was a rapid increase in the use of hormone therapy in the United States from 1994 to 1999. The significantly increased use of hormone therapy for high-risk patients in the United States reflects the penetration and growing acceptance of clinical trial results that have demonstrated the efficacy of these treatment approaches (32, 33). The randomized Radiation Therapy Oncology Group 8610 trial demonstrated an increase in disease-free survival at 2 years (76% vs. 62% survival) for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiation compared to those treated with radiation therapy alone (33). In Japan, hormone therapy was administered to approximately 90% of patients with high-risk disease, and these high rates of hormone therapy have continued for several years. Therefore, radiotherapy in conjunction with hormone therapy appears to be an accepted approach for the unfavorable risk group in Japan and in the United States.

CONCLUSIONS

By comparing the PCS results of 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, we can delineate changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. Study data indicate a trend toward increasing early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipments, suggesting that radical EBRT is gaining acceptance as a first-line treatment for prostate cancer in Japan. Also, our results indicate that patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. In the future, to optimize the delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted. Also, repeat surveys and point-by-point comparisons of results from other countries, such as the United States, will demonstrate how EBRT for prostate cancer has been developed and optimized for patients in Japan.

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特集

乳癌治療

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