Table 3. Treatment combinations according to age groups

Treatment combination	Total	Age group			Institutions	
		<65 y (n = 144)	65–74 y (n = 141)	≥75 y (n = 164)	Academic (n = 358)	Nonacademic (n = 263)
RT with chemotherapy						
Total	393 (63)	180 (74)	155 (73)	58 (34)	240 (67)	153 (58)
Definitively	244 (39)	87 (36)	101 (47)	56 (34)	128 (36)	116 (44)
With surgery	148 (24)	92 (38)	54 (25)	2 (1)	111 (31)	37 (14)
Unknown	1	1	0	0	1	0
RT without chemotherapy						
Total	219 (35)	59 (24)	56 (26)	104 (63)	111 (31)	108 (41)
Definitively	169 (27)	26 (11)	42 (20)	101 (62)	83 (23)	86 (33)
With surgery	50 (8)	33 (14)	14 (7)	3 (2)	28 (8)	22 (8)
Unknown	0	0	0	0	0	0
Unknown about chemotherapy						
Total	9 (1)	5 (2)	2 (1)	2 (1)	7 (2)	2 (1)
Definitively	2	1	1	0	2 (1)	0
With surgery	6 (1)	3 (1)	1	2 (1)	4 (1)	2 (1)
Unknown	1	1	0	0	1	0

Abbreviation: RT = radiotherapy.
Values are number (percentage).

in multidisciplinary management of this disease. The Japanese PCS group conducted two large surveys in the 1990s and reported patient backgrounds and RT practices for esophageal cancer (5, 6). A summary of patient backgrounds and treatments from three Japanese PCSs and two U.S. PCSs is shown in Table 6.

The incidence of adenocarcinoma of the esophagus has rapidly increased in the United States since the 1970s and has accounted for approximately half of esophageal cancers in recent years (8, 9). The U.S. PCS for 1996–1999 reported the ratio of adenocarcinoma and SCC as 48.7% and 49.6%, respectively (3). Some reports from European countries also showed an increasing incidence of adenocarcinoma (10). On the other hand, this trend is not observed in Asian countries. A recent report based on the cancer registry in Japan showed the ratio of SCC to adenocarcinoma to be 26:1 (11). Preliminary results of the Korean PCS reported that 96% of investigated patients had SCC histology (12). Consistent with the previous two Japanese PCSs, 99% of patients in this study had SCC. Although adenocarcinoma mainly arises in the lower esophagus near the esophagogastric junction, the most common location of the main lesion for SCC is the midthoracic esophagus. More than half of patients had the main lesion in the midthoracic esophagus in this study. Differences in tumor histology and main tumor location may have an influence on treatment strategies and results (*i.e.* type of surgery, setting of target volume of RT, and adverse effects of the treatments).

The discrepancy between the United States and Japan was also identified in the pretherapy evaluations. Both endoscopy and esophagram were the standard evaluation methods for esophageal cancer in Japan, but approximately one third of patients did not receive an esophagram in the United States. Barium study is the traditional and relatively easy method for evaluating the gastrointestinal tract and is used for mass screening for gastric cancer in Japan. Because most gastroenterologists are skilled in doing esophagrams in Japan, it was routinely used for evaluation of esophageal cancer. Endoscopic ultrasound is the most accurate method to define both T and N staging of esophageal carcinoma in the current staging system (13). The current International Union Against Cancer staging system adopted depth of tumor invasion for T staging, which increased use of endoscopic ultrasound in each country.

Since the Intergroup study reported by Cooper *et al.* (14) showed the superiority of CRT over RT alone for esophageal cancer, the application of CRT has increased in the United States (3, 4). The ratio of using chemotherapy in combination with RT in Japan has also increased, from 40% in PCS 1995–1997 to 63% in PCS 1999–2001. Most of the CRT patients in Japan used cisplatin and 5-fluorouracil for chemotherapy. One reason is that taxanes had not been approved for esophageal cancer in Japan until 2003. The other reason was that not enough evidence was shown regarding the use of taxanes in CRT for esophageal cancer in the 1990s.

In the U.S. PCS, median total external RT dose was 50.4 Gy (1, 3). However, our data showed the median total external dose in Japan to be 60 Gy, and it was same for RT-only patients and definitive CRT patients. Not many clinical trials have investigated the total dose in CRT for esophageal cancer. The standard dose used in the United States is considered to be based on the results of a Phase III trial (INT 0123) showing no benefit of higher radiation on survival or locoregional control (15). After publication of the results of INT 0123, clinical studies investigating total RT dose in esophageal cancer in the United States seem to have been stopped. On the other hand, some Phase II studies conducted in Japan in the 1990s testing the efficacy of CRT for esophageal cancer used a total dose of 60 Gy, and preliminary results showed excellent outcomes (16, 17). Ohtsu *et al.* (16) studied 44 patients

Table 4. External RT parameters in nonsurgery patients

Characteristic	Age group <65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)	Total (n = 621)	p
Total external RT dose (Gy)					—
<30	4 (4)	7 (5)	6 (4)	17 (4)	
30.1–40	14 (12)	13 (9)	9 (6)	36 (9)	
40.1–50	7 (6)	12 (9)	13 (8)	32 (8)	
50.1–60	40 (35)	40 (28)	47 (30)	127 (31)	
60.1–70	40 (35)	66 (47)	77 (49)	183 (44)	
>70	9 (8)	3 (2)	4 (3)	16 (4)	
Missing	—	—	1	1	
Median (Gy)	60.0	60.0	60.0	60.0	
Hyperfractionation					0.500
Done	14 (12)	25 (18)	25 (16)	64 (16)	
Not done	100 (88)	116 (82)	132 (84)	348 (84)	
Missing	—	—	—	—	
Initial longitudinal field size (cm)					0.001
≤10.0	3 (3)	14 (10)	25 (16)	42 (10)	
10.1–15.0	21 (19)	39 (28)	53 (34)	113 (28)	
15.1–20	35 (31)	48 (34)	47 (30)	130 (32)	
20.1–25	34 (30)	26 (19)	18 (12)	78 (19)	
≥25.1	19 (17)	13 (9)	12 (8)	44 (11)	
Missing	2	1	2	5	
Mean (cm)	20	17	15	17	
Mediastinal nodal area irradiation					0.063
Done	96 (86)	110 (79)	116 (74)	322 (79)	
Not done	16 (14)	29 (21)	41 (26)	86 (21)	
Unknown	—	—	—	—	
Missing	2	2	—	4	
Supraclavicular nodal area irradiation					
Done	41 (37)	31 (22)	27 (17)	99 (24)	0.003
Not done	70 (63)	108 (78)	129 (82)	307 (75)	
Unknown	—	—	1 (1)	1	
Missing	3	2	—	5	
Upper abdominal nodal area irradiation					0.050
Done	32 (29)	33 (24)	25 (16)	90 (22)	
Not done	79 (71)	106 (76)	130 (83)	315 (77)	
Unknown	—	—	2 (1)	2 (1)	
Missing	3	2	—	5	
Field reduction					0.517
Done	87 (78)	104 (74)	111 (71)	302 (74)	
Not done	24 (21)	35 (25)	45 (29)	104 (25)	
Unknown	1 (1)	1 (1)	1 (1)	3 (1)	
Missing	2	1	—	3	

Abbreviation: RT = radiotherapy.
Values are number (percentage).

with T4 and/or M1 by lymph node treated with 60 Gy of external RT and concurrently administered cisplatin and 5-fluorouracil. Three-year overall survival was 23%. This result, published in 1999, may have impacted clinical practice during this study period. Supported by the results of this study, a total dose of 60 Gy in CRT might become standard practice in Japan. Ishikura *et al.* (18) reported substantial late pulmonary and cardiac toxicities by 60 Gy of thoracic CRT with a conventional opposed two-beam technique. Additional investigation regarding the optimal total dose of CRT for esophageal cancer with modern RT techniques is warranted.

Patients aged ≥75 years account for 26% of all patients in this study. Some characteristics of patient backgrounds and differences of treatment for elderly patients are apparent from this study. More early-stage patients and more low-KPS patients were included in the elderly group than in the middle or younger age groups. Elderly patients were not frequently treated by multimodality treatments in combination with surgery and chemotherapy but rather by RT alone. Although surgery in combination with CRT or chemotherapy is the standard treatment for operable esophageal cancer, patients with a low performance status or with comorbid disease were medically unfit for surgery. Radiotherapy alone might be frequently chosen as the most noninvasive treatment for elderly esophageal cancer patients. Meanwhile, 34% of elderly patients received

Table 5. Backgrounds and radiotherapy parameters of patients who received definitive CRT, RT alone, or preoperative CRT

Parameter	Definitive CRT (n = 241)	RT alone* (n = 146)	Preoperative CRT (n = 86)
Male/female	89/11	80/20	86/14
Age (y), median	68	78	63
KPS >90	29	34	36
Main tumor lesion, upper	21	18	20
Stage 0–IIb	36	34	29
Stage III–IV	62	58	71
Total external RT dose (Gy)			
≤30	4	5	35
30.1–40	11	4	33
40.1–50	7	10	12
50.1–60	32	31	12
60.1–70	43	45	10
≥70.1	4	4	
Median (Gy)	60	60	40
Initial longitudinal† field size (cm)			
≤10	5	17	3
10.1–15.0	23	36	27
15.1–20.0	36	26	37

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.
Values are percentages except where noted.
* RT without chemotherapy.
† Craniocaudal direction.

definitive CRT. There are not enough data available regarding the efficacy of chemoradiation in elderly or low-KPS patients (19), and criteria for reducing RT dose and chemotherapy dose for these patients have not been established. The intensity of chemotherapy used for CRT was not clearly investigated in this study, but regarding RT field, a narrow field excluding the supraclavicular area was generally preferred for elderly patients. Further clinical investigations evaluating the role of CRT and RT in elderly esophageal cancer patients are needed.

In conclusion, this PCS describes patient backgrounds and general patterns of RT practice for esophageal cancer

Table 6. Comparison of patient backgrounds and treatment combinations among three Japanese PCSs and U.S. PCSs

Parameter	PCS 1992–1994 (n = 561)	PCS 1995–1997 (n = 776)	PCS 1999–2001 (n = 621)	U.S. PCS 1992–1994 (n = 400)	U.S. PCS 1996–1999 (n = 414)
Academic/nonacademic	46/54	62/38	58/42	51/49	NA
Median age (y)	66	67	68	66.7	64
Male/female	86/14	85/14	87/13	76.5/23.5	77/23
KPS ≥90	33	27	35	47	56
Esophagram done	NA	92	93	69	64
Endoscopy done	NA	91	96	94	96
Endoscopic ultrasound done	NA	21	27	4	18
Clinical Stage I by AJCC, 1983 version	15	19	20	15	16
Squamous cell carcinoma	99	100	99	61.5	49
Main tumor location, middle thorax	NA	62	55	NA	NA
External RT done	99	99	99	Nearly all	100
External beam energy >6 MV	85	78	92	>76	NA
Median fraction external RT dose (Gy)	2.0	2.0	2.0	1.8	1.8
Median total external RT dose (Gy)	60.0	60.0	60.0	50.4	50.4
Brachytherapy done	10	12	6	8.5	6
Chemotherapy done	35	40	63	75	89
Preoperative RT + CT followed by surgery	16	9	16	14.5	27
Surgery followed by RT + CT	22	19	18	11	6
Definitive CRT	22	25	39 5	4	56
RT alone without surgery or CT	34	44	27	20	10

Abbreviations: PCS = Patterns of Care Study; NA = not applicable; KPS = Karnofsky performance status; AJCC = American Joint Committee on Cancer; RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy.
Values are percentages except where noted.

in Japan. Tumor histology and standard RT dose were different between the United States and Japan. Care should be taken when comparing data from these two countries. This study also revealed the treatment characteristics for elderly esophageal cancer patients. Repeated surveys will demonstrate the trends for esophageal cancer treatment in Japan and will provide useful data for international comparison.

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Radiotherapy for patients with localized hormone-refractory prostate cancer: results of the Patterns of Care Study in Japan

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Study Type – Therapy (cohort)
Level of Evidence 2b

OBJECTIVE

To evaluate the clinical results of radiotherapy (RT) for patients with regionally localized hormone-refractory prostate carcinoma (HRPC).

PATIENTS AND METHODS

As part of a Patterns of Care Study in Japan, a nationwide survey was conducted of RT for patients with prostate adenocarcinoma. We reviewed the detailed information of 140 patients with regionally localized HRPC who received RT between 1996 and 1998, and between 1999 and 2001, in 117 randomly selected institutes in Japan. The median (range) age of the patients was 74 (51–94) years, and their tumours were defined as well (14), moderately (51) or poorly (54) differentiated, or of unknown differentiation (21). The median (range) interval between hormonal therapy (HT) and RT was 32.5 (1.1–168.4) months. Ninety-five patients had T3-4 tumours and 28 had regional lymph node metastases before treatment. The median (range) prostate-specific antigen levels before the initial HT and before RT were 35.0 (1.5–276) and 10.0 (0.06–760.3) ng/mL, respectively. External beam RT was administered, with a median total dose of 66 Gy; 70 patients (50%) received pelvic irradiation.

RESULTS

At a median follow-up of 20.7 months, the 5-year overall and clinical progression-free survival rates (95% confidence interval) were 48.1 (36–60)% and 36.7 (26–47)%, respectively. Although there were distant metastases in 46 patients, only six had local progression. There was late morbidity of grade ≥3 in six patients.

CONCLUSION

To the best of our knowledge, this study comprises the largest series of regionally localized HRPC treated with RT reported to date. RT might have a limited role for HRPC, because in most patients RT failed, with distant metastasis.

KEYWORDS

hormone-refractory prostate cancer, Patterns of Care Study, radiotherapy

INTRODUCTION

Although hormonal therapy (HT) is an effective treatment for patients with prostate cancer, many relapse and become resistant to further hormone manipulation within a few years. The androgen-dependent period in patients with metastatic disease lasts for a median of 14–30 months [1]. For patients with nonmetastatic prostate cancer treated with continuous androgen deprivation, the cause-specific survival rates at 5 years have been reported to be 70–92% [2–4]. However, despite the favourable clinical outcome in the short term, the median time to biochemical progression is only 19–36 months for patients with regionally localized advanced prostate cancer [5]. Thus, HT has been used in Europe and North America primarily to provide temporary relief for advanced cancer. On the other hand, the CaPSURE data, which was reported in 2003 and comprises analyses of 3439 cases, recently showed that the rate of primary HT on localized prostate cancer increased remarkably, from 4.6% in 1989 to 14.2% in 2001 [6].

By contrast, HT has been commonly used in Japan for those patients with high-risk prostate cancer, based on the clinical experience of the treating physicians [7–9]. According to the Japanese Prostate Cancer survey, 75% of 16 147 patients who were newly diagnosed with prostate cancer in 395 institutes in Japan from 2001 to 2002 were treated with HT in some form (HT alone,

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Variable	Median (range), n or n (%)
Age, years	74 (51–94)
Observation period, months	20.7 (1–103)
Reason for RT	
Clinical failure	55
PSA failure	85
Differentiation of tumours	
Well	14 (10.9)
Moderately	51 (39.5)
Poorly	54 (41.9)
Unknown	10 (7.8)
Missing data	11
T stage	
0–1	2 (1.5)
2	21 (15.8)
3	59 (44.4)
4	36 (27.1)
Unknown	15 (11.3)
Missing data	7
N stage	
0	84 (65.1)
1	28 (21.7)
Unknown	17 (13.2)
Missing data	11
PSA level, ng/mL	
Before treatment	35.0 (1.5–276)
<10	11 (12.2)
10.0–19.9	11 (12.2)
≥20	68 (75.6)
Missing data	50
Before radiotherapy	10.0 (0.06–760.3)
<10	59 (48.8)
10.0–19.9	30 (24.8)
≥20	32 (26.4)
Missing data	19

TABLE 1 The characteristics of the 140 patients

neoadjuvant or adjuvant settings) [10]. Furthermore, the survey showed that 66% of the patients with localized early prostate cancer were treated with HT alone. Although the prevalence of prostate cancer in Japan has been remarkably lower than that in Europe and North America, in Japan there has been an overwhelming increase in morbidity and mortality from prostate cancer over the last 40 years [11].

Therefore, a substantial number of patients with localized disease before HT will develop hormone-refractory prostate cancer (HRPC) in terms of increasing PSA levels or overt clinical disease. Zagars *et al.* [12] showed that local progression is one of the most common types of disease progression in patients with HRPC, but there are only a few reports to date on the efficacy of radiotherapy (RT) in the management of regionally localized HRPC in small series of patients [13–16]. Patients with HRPC can be treated with RT in Japan [17], even though the role of RT for patients with localized HRPC has not yet been well established.

The Patterns of Care Study (PCS), a type of study developed in the USA as a quality-assurance programme, was conducted in Japan in an attempt to obtain data on the national standards of the use of RT for several diseases, including prostate cancer [18]. The Japanese PCS Working Group on Prostate Cancer conducted the first and second nationwide process surveys of patients with prostate cancer who received RT between 1996 and 1998 (PCS96-98) and between 1999 and 2001 (PCS99-01). Our group previously reported the preliminary outcomes of RT for patients with localized HRPC in Japan, based on the results from PCS96-98 [16], and documented that RT had a high rate of local control, but that it failed in some patients who developed distant metastasis. In the present report, we provide an analysis of both PCS96-98 and PCS99-01 to evaluate the outcome of patients with HRPC who received RT, and to assess the role of RT in patients with localized HRPC.

PATIENTS AND METHODS

The standard methods used in data collection for a national process survey were described previously in detail [16,18]. Briefly, the PCS survey used a stratified two-stage cluster sampling method. An external audit team of radiation oncologists surveyed 84 institutes in PCS96-98 and 76 institutes in PCS99-01, respectively [19]. PCS96-98 and PCS99-01 stratified these institutions into either academic (university hospital or cancer centre) or non-academic institutions (other hospitals) according to a facility master list created by the Japanese Society of Therapeutic Radiation Oncology in 1997 and 2001, respectively. Search criteria were as follows: (i) the patients had adenocarcinoma of the prostate with no distant metastases; (ii) the patients received RT during either 1996–1998 or 1999–2001; and (iii) the patients had not been diagnosed with any other malignancy or treated with RT previously [17].

The detailed information of 839 patients treated with RT was collected in PCS96-98 and PCS99-01. For the purposes of the present study, we selected the 140 patients (16.7%) from the two surveys who had regionally localized HRPC according to the following definition: (i) patients who had not received surgical treatment for prostate cancer; (ii) patients who had received HT initially; (iii) patients who had consecutive increasing PSA levels or had clinical loco-regional failure after initial HT. A DRE and diagnostic imaging, e.g. CT, MRI or bone scintigraphy were assessed before HT for staging and before RT for re-staging, according to the TNM staging system (1997).

The characteristics of the patients are shown in Table 1. Before RT, 55 patients had clinical progression and the other 85 had PSA failure alone. The median (range) interval between HT and RT was 32.5 (1.1–168.4) months. Biopsy Gleason scores were not available for most

TABLE 2 Treatment characteristics

Treatment	Median (range), n/N or n (%)
HT	
Interval between HT and RT, months	32.5 (1.1–168.4)
Method of androgen ablation*†	
Orchidectomy	39/140
Oestrogen agent	43/140
LH-RH agonist	113/140
Antiandrogen	102/140
RT	
Beam energy, MV	
Cobalt 60	1 (0.8)
Photons <10	27 (22.9)
Photons ≥10 to <18	83 (70.3)
Photons ≥18	7 (5.9)
Missing data	22
Technique	
AP/PA or LR/RL only	25 (21.2)
≥3 fields	59 (50.0)
Moving beam/dynamic conformal	26 (22.0)
Others/unknown	8 (6.8)
Missing data	22
Pelvic irradiation	
Yes	70 (50.0)
No	70 (50.0)

*37 patients (26.4%) were also treated with chemotherapy including estramustine. †Some patients had more than one treatment. AP/PA, anterior-posterior; LR/RL, left-right.

FIG. 1. Overall and clinical progression-free survival curves of patients with HRPC after RT.

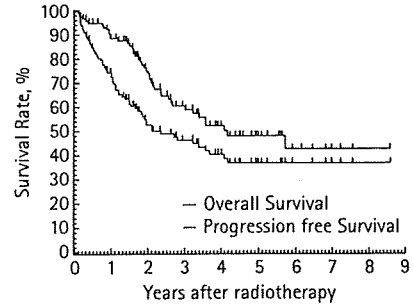

TABLE 3 Patterns of recurrence in 54 patients

Pattern	*n* (%)
Local	3 (6)
Regional	4 (7)
Local + regional	1 (2)
Local + distant	2 (4)
Regional + distant	6 (11)
Distant	38 (70)
Others*	12

**including patients who died from prostate cancer but details of disease progression were unknown.*

TABLE 4 The rates of morbidity (NCI-CTC AE v3)

Morbidity	Grade 2	Grade 3
Rectal toxicity, *n*		
Bleeding	4	5
Stricture	0	1
Urinary toxicity, *n*		
Ureteric obstruction	1	0
Urethral stricture	4	0
Incontinence	2	0

patients in this series, but the percentage of patients with poorly differentiated adenocarcinomas, considered to be an approximation to Gleason 8–10 tumours, was >40%. The HT and RT methods are shown in Table 2. Chemotherapy was administered in 37 patients (26.4%), 12 of whom received estramustine, although the chemotherapy regimens varied, including cisplatin, 5-fluorouracil, etoposide, etc. The total RT doses varied, and the median (range) dose was 66 (10–90) Gy; the median dose per fraction was 2 (1.5–3) Gy.

The outcome measure used in the present analysis was defined as the interval from the first day of RT to clinical progression and to death, using the Kaplan-Meier product-limit method. Distributions were compared using a univariate analysis, with a log-rank statistic, and multivariate analysis with Cox_s proportional hazard model, using the Statistical Analysis System at the PCS data centre at Osaka University [20]. In all tests, $P \leq 0.05$ was considered to indicate significance. Acute and late morbidities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC AE) version 3; late morbidities occurring >3 months after RT are described.

RESULTS

With a median (range) follow-up of 20.7 (1–103) months after RT, 41 patients died from prostate cancer and three died from intercurrent disease; the cause of death was unknown in one patient. Sixty-six patients were identified as having clinical progression, including 12 who died from prostate cancer with no detailed information on their clinical progression. The sites of recurrence are shown in Table 3. Local failure occurred in only six of the patients who had disease relapse. One of the patients with local recurrence had regional lymph node metastasis, and the other two had distant metastasis. Forty-six patients had distant metastasis, including two with local failure and six with regional lymph node recurrence. Twelve patients received irradiation of <50 Gy, only one of whom had local failure. Sixteen patients had a continuous increase in PSA level with no clinical progression after RT. The Kaplan-Meier estimates of the overall and clinical progression-free survival rates (95% CI) at 5 years were 48.1 (36–60)% and 36.7 (26–47)%, respectively (Fig. 1).

Patients with grade ≥2 toxicity according to NCI-CTC AE are shown in Table 4; although none had late toxicity of grade ≥4, five had rectal bleeding and were treated with transfusion or laser coagulation. One patient received surgical treatment because of a severe rectal stricture. No patients had genitourinary toxicity of grade ≥3.

Univariate analysis showed that Karnofsky performance status (KPS, $P = 0.004$), T stage ($P = 0.023$), N stage ($P < 0.001$) and total dose ($P = 0.001$) were statistically significant factors for overall survival, while a multivariate analysis showed that age

TABLE 5 Uni- and multivariate analyses for prognostic factors of overall survival

Factor	*P*		
	Univariate	Multivariate	Hazard ratio
Clinical failure before RT, Yes vs no	0.09	0.30	5.183
KPS, <80 vs ≥80	0.004*	0.60	1.356
Age, years, <70 vs ≥70	0.92	0.046*	4.662
T stage, T0–2 vs T3–4	0.02*	0.07	3.326
N stage, N0 vs N1	<0.001*	0.01*	4.953
Differentiation of tumours, Well/moderately vs poorly	0.39	0.92	0.953
PSA level, ng/mL, <20 vs ≥20			
Before treatment	0.62	0.30	0.505
Before RT	0.50	0.36	1.791
Chemotherapy, yes vs no	0.09	0.06	0.304
Pelvic irradiation, yes vs no	0.10	0.75	1.175
Total dose, Gy, <60 vs ≥60	0.001*	0.54	0.630

**Statistically significant.*

($P = 0.046$) and N stage ($P = 0.01$), were significant prognostic factors (Table 5).

DISCUSSION

In the present study we assessed the clinical results of RT for patients with regionally localized HRPC, and compared the results with those from previous analyses [13–15]. Lankford *et al.* [13] retrospectively analysed the results of RT for 29 patients with HRPC, and reported that the actuarial local failure rate at 4 years after locoregional RT was 39%, although 80% of patients had disease progression or an increasing PSA level, and the actuarial survival at 4 years was 39%. They concluded that RT was useful to obtain long-term local control, in addition to relief of symptoms [13]. Akimoto *et al.* [15] showed the usefulness of external RT for 53 patients with node-negative, localized HRPC. These patients were treated with external RT using the oblique four-field technique, at a total dose of 69 Gy (the fractional dose was 3 Gy three times weekly). In their study, only two patients had local failure at the first recurrent site, in contrast to 13 with bone or lymph node metastases, and the 5-year cause-specific survival rate was 87%. Sanguineti *et al.* [14] assessed the results of external RT (median dose 70 Gy) in 29 patients with prostate-confined HRPC, with mean (SD) estimates of locoregional control rate, actuarial incidence of distant metastasis and overall survival at 5 years being 89 (7)%, 68 (9)% and 28 (9)%, respectively; they concluded that external RT gave excellent local control, although most patients developed distant metastases within a few years of RT. In the present series, only six patients had local failure and 46 had distant metastasis. The overall survival rate at 5 years was 48.1%. However, Oeffelein *et al.* [21] showed that the median survival after HRPC developed in patients initially staged with and without bone metastasis, who did not receive definitive RT or surgery, was 40 and 68 months, respectively. Thus, RT might have only a palliative role in patients with localized HRPC because in most it failed, with distant metastasis.

However, a significant percentage of patients with HRPC who are treated with RT were well controlled, both in the previous and in the present analyses. It is important to accurately identify patients with no subclinical distant metastasis for definitive success with RT. Sanguineti *et al.* [14] investigated predictors of distant metastasis, and reported that patients with a low Gleason score at diagnosis, lower PSA level at RT, and advanced age, were less likely to develop distant metastasis. Akimoto *et al.* [15] found, in a univariate analysis, that the PSA doubling time (DT), PSA level before RT and Gleason score were significantly associated with clinical relapse, almost of which were distant metastasis, while only the PSA level before RT was significant in a multivariate analysis, leading them to conclude that RT should be started before the PSA level reaches ≥15 ng/mL, or at least < 20 ng/mL, to obtain the maximum benefit of RT. Furthermore, other previous analyses showed that the PSADT, with an increasing PSA level after prostatectomy, HT and RT is associated with disease relapse, indicating that patients with a shorter PSADT have a greater incidence of systemic progression or distant metastasis than those with a slowly increasing PSA level [22–24]. These patients with a low risk of distant failure should receive definitive RT.

Lankford *et al.* [13] found that RT doses of >60 Gy were associated with symptom-free local control, and Sanguineti *et al.* [14] recommend total doses of least 60–66 Gy at 2 Gy per fraction, although they found that further dose increase was not worthwhile. In the present analysis, although the symptoms for each patient were not available, a total dose of >60 Gy was also a significant prognostic factor for overall survival in the univariate analysis. However, Kawakami *et al.* [8] stated that palliative doses of 27–38 Gy, in 10 patients with HRPC presenting with urinary retention and/or gross haematuria, were effective for local control, with low invasiveness and minimal complications. They recommended that, if local progression is symptomatic, palliative irradiation should be initiated as soon as possible. Furthermore, Kraus *et al.* [25] reported that 33 patients with locally invasive prostate cancer, including HRPC, who received 4000–5000 rad of irradiation with palliative intent, were free of their symptoms. In the present series, 12 patients received doses of <50 Gy, only one of whom had local failure, indicating that a relatively low dose might be sufficient for local control in patients with HRPC. Further study is necessary to establish appropriate irradiation doses for patients with HRPC.

In conclusion, to the best of our knowledge the present study on the efficacy of RT is the largest series reported to date of patients with regionally localized HRPC, although there are some shortcoming, i.e. the lack of data on patient symptoms, Gleason scores, and varying RT techniques and doses. RT for patients with localized HRPC seems to have a limited role for prolonging overall survival because in most patients it failed, with distant metastasis. Further examination is required to establish the appropriate role of RT.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HRPC**, hormone-refractory prostate cancer; **RT**, radiotherapy; **HT**, hormone therapy; **KPS**, Karnofsky performance status; **NCI-CTC AE**, National Cancer Institute Common Toxicity Criteria for Adverse Events; **PCS**, Patterns of Care Study; **DT**, doubling time.

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CLINICAL INVESTIGATION **Prostate**

EXTERNAL BEAM RADIOTHERAPY FOR CLINICALLY LOCALIZED HORMONE-REFRACTORY PROSTATE CANCER: CLINICAL SIGNIFICANCE OF NADIR PROSTATE-SPECIFIC ANTIGEN VALUE WITHIN 12 MONTHS

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Purpose: To analyze retrospectively the results of external beam radiotherapy for clinically localized hormone-refractory prostate cancer and investigate the clinical significance of nadir prostate-specific antigen (PSA) value within 12 months (nPSA12) as an early estimate of clinical outcomes after radiotherapy.

Methods and Materials: Eighty-four patients with localized hormone-refractory prostate cancer treated with external beam radiotherapy were retrospectively reviewed. The total radiation doses ranged from 30 to 76 Gy (median, 66 Gy), and the median follow-up period for all 84 patients was 26.9 months (range, 2.7–77.3 months).

Results: The 3-year actuarial overall survival, progression-free survival (PFS), and local control rates in all 84 patients after radiotherapy were 67%, 61%, and 93%, respectively. Although distant metastases and/or regional lymph node metastases developed in 34 patients (40%) after radiotherapy, local progression was observed in only 5 patients (6%). Of all 84 patients, the median nPSA12 in patients with clinical failure and in patients without clinical failure was 3.1 ng/mL and 0.5 ng/mL, respectively. When dividing patients according to low (<0.5 ng/mL) and high (≥0.5 ng/mL) nPSA12 levels, the 3-year PFS rate in patients with low nPSA12 and in those with high nPSA12 was 96% and 44%, respectively ($p < 0.0001$). In univariate analysis, nPSA12 and pretreatment PSA value had a significant impact on PFS, and in multivariate analysis nPSA12 alone was an independent prognostic factor for PFS after radiotherapy.

Conclusions: External beam radiotherapy had an excellent local control rate for clinically localized hormone-refractory prostate cancer, and nPSA12 was predictive of clinical outcomes after radiotherapy. © 2009 Elsevier Inc.

Hormone-refractory, Prostate cancer, nPSA12, Radiotherapy, Prognostic factor.

INTRODUCTION

Androgen ablation is an effective treatment approach for prostate cancer and has been used as one of the primary treatments for localized disease or palliative treatment for systemic disease (1, 2). In Japan in particular, androgen ablation has frequently been used because most Japanese patients with prostate cancer have had high-risk disease and hormonal therapy is frequently preferred as the primary therapy (3, 4). Although almost all prostate cancers initially respond well to hormonal therapy, the majority eventually lose their hormone

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Table 1. Patient characteristics

Age (y) (median, 73.3)	
<75	51
≥75	33
KPS (%)	
≤80	45
>80	35
Unknown	4
T stage (1997 UICC)	
T0–2	18
T3–4	66
N stage (1997 UICC)	
N0	58
N1	10
Unknown	16
Pretreatment PSA (ng/mL)	
Median (range)	9.7 (0.06–760.3)
<4	14
≥4	69
Unknown	1
Gleason combined score	
≤6	5
>6	13
Unknown	66
Differentiation	
Well/moderately	38
Poorly	31
Unknown	15

Abbreviations: KPS = Karnofsky performance status; UICC = International Union Against Cancer; PSA = prostate-specific antigen.

sensitivity and progress (5). In the absence of an effective therapy for hormone-refractory prostate cancer, patients will die within approximately 12–18 months after the diagnosis of hormone-refractory prostate cancer (6). Among these patients, however, some will develop local progression without systemic diseases. Although the optimal treatment approach for clinically localized hormone-refractory prostate cancer has not yet been established, radiotherapy may be considered the treatment of choice to treat local progression with curative intent or to release urinary obstructive symptoms as a palliative treatment (7–9). However, little information exists on the efficacy of radiotherapy for localized hormone-refractory disease. Moreover, there is also minimal information regarding the clinically useful markers of recurrence risk for localized hormone-refractory prostate cancer treated with radiotherapy.

For patients with untreated prostate cancer, prostate-specific antigen (PSA) has been used as an important tool for prostate cancer screening and as a marker for treatment response and disease recurrence (10, 11). The PSA nadir (nPSA) after radiotherapy has been shown to predict biochemical failure (12, 13), distant metastases (14, 15), cause-specific mortality (16, 17), and overall mortality (17). However, the nPSA usually takes several years to occur, even as long as 8–10 years in some patients, and as a consequence nPSA has little practical clinical value. It would be ideal to identify a surrogate nPSA that describes the lowest PSA value achieved during a well-defined, relatively short interval after completion of radiotherapy. Recently, time-limited survey of PSA, such as nPSA value within 12 months (nPSA12), has been reported to be an early predictor of biochemical failure, distant metastases, and mortality that is independent of radiotherapy dose and other determinants of outcome after radiotherapy for previously untreated localized prostate cancer (10, 11).

Because nPSA12 has been shown to be a useful predictor of treatment outcome for untreated localized prostate cancer treated with radical radiotherapy, we hypothesized that nPSA12 may also have potential applications in the monitoring of localized hormone-refractory prostate cancer treated with radiotherapy. In the present study we analyzed the treatment results of external beam radiotherapy for localized hormone-refractory prostate cancer. Next, we examined the nPSA12 in patients with hormone-refractory prostate cancer treated with radiotherapy and investigated whether nPSA12 could be a prognostic factor of clinical outcomes for these patients.

METHODS AND MATERIALS

We used detailed data from patients with clinically localized hormone-refractory prostate cancer who were included in the Japanese Patterns of Care Study (PCS). The PCS, which has been developed in the United States as a quality assurance program, was conducted in Japan in an attempt to obtain data on the national standards of radiotherapy for several diseases, including prostate cancer (18). The Japanese PCS Working Subgroup of Prostate Cancer initiated a nationwide process survey for patients who underwent radiotherapy between 1996 and 1998. Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted. We have previously reported the results of the first and second PCS surveys with respect to external beam radiotherapy for prostate cancer patients (19–24).

The PCS methodology has been described previously (18, 25, 26). In brief, the PCS surveys were extramural audits that used a stratified two-stage cluster sampling design. The PCS surveyors consisted of 20 radiation oncologists from academic institutions, and one radiation oncologist collected data by reviewing patients' charts from each institution. 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: evidence of distant metastasis, concurrent or prior diagnosis of any other malignancy, or prior radiotherapy. The PCS data used in the present study are from two Japanese national surveys conducted to evaluate prostate cancer patients treated with radiotherapy in the 1996–1998 and 1999–2001 PCS surveys. Of the 839 patients constituting the 1996–1998 and 1999–2001 PCS survey populations, a total of 154 patients with regionally localized hormone-refractory prostate cancer were identified. Of these, 70 patients with insufficient nPSA12 data were excluded; a total of 84 patients with measurable nPSA12 were subjected to this analysis. The disease characteristics of these 84 patients, such as tumor stage and pretreatment PSA levels, were not significantly different compared with those of the 70 patients having insufficient data for nPSA12. All 84 patients received androgen ablation alone initially, followed by radiotherapy for local or biological progression in the absence of distant metastases.

Table 1 shows the patient characteristics for all 84 patients. Most patients had advanced disease at initial treatment. Pretreatment PSA value was defined as the PSA value before initial hormonal

Table 2. Treatment characteristics

Treatment	*n* (%)
Hormonal therapy	
Orchiectomy	19 (12)
Estrogen agent	24 (28)
LHRH agonist	78 (92)
Antiandrogen	60 (71)
Chemotherapy	
Yes	23 (27)
No	58 (69)
Unknown	3 (4)
Radiotherapy	
Radiation field	
WP plus boost	34 (40)
Prostate only	50 (60)
Total radiation dose (Gy)	
<60	12 (14)
>60	72 (86)
CT-based treatment planning	
Yes	17 (20)
No	49 (59)
Unknown	18 (21)
Conformal therapy	
Yes	23 (27)
No	44 (53)
Unknown	17 (20)

Abbreviations: LHRH = luteinizing hormone-releasing hormone; WP = whole pelvis.

treatment, and preradiotherapy PSA value was defined as the PSA value just before radiotherapy.

Methods of treatment are shown in Table 2. Hormonal therapy was administered alone or in combination with orchiectomy, estrogen agent, luteinizing hormone-releasing hormone agonist, or antiandrogen. The median duration of hormonal therapy before radiotherapy was 34.4 months (range, 0.2–164.8 months). Regarding chemotherapy, 23 patients (28%) were also treated with chemotherapy, such as estramustine and 5-fluorouracil, but no patients received docetaxel or paclitaxel-containing chemotherapy.

Regarding radiotherapy, most of the patients were treated with ≥10 MV linear accelerator and also treated with four or more portals. The median radiation dose delivered to the prostate was 66 Gy (range, 30–76 Gy), and the median dose per fraction was 2.0 Gy (range, 1.5–3.0 Gy). In the present study there were no definitive treatment policies for hormone-refractory prostate cancer, and radiation field was determined by the respective physicians at each institution. Thirty-four patients (40%) received treatment to the pelvic nodes in addition to prostate, and the remaining 50 patients (60%) received irradiation only to the prostate. Regarding lymph node status, 8 of 10 patients (80%) with clinically positive lymph nodes received treatment to the pelvic nodes in addition to prostate.

The nPSA12 was defined as the lowest PSA level achieved during the first year after completion of radiotherapy. The median number of PSA evaluations within 12 months after radiotherapy was 4 (range, 1–12) in all 84 patients. Median follow-up of all patients was 26.9 months (range, 2.7–77.3 months), and all patients without clinical failure had at least 1 year of follow-up. Patients were categorized as having progression after radiotherapy if they developed local, pelvic nodal, or distant failure.

Statistical analyses were performed using the Statistical Analysis System (SAS Institute, Tokyo, Japan) at the PCS statistical center (27). Overall and progression-free survival (PFS) rates were calculated actuarially according to the Kaplan-Meier method (28) and were measured from the start of radiotherapy. Differences between groups were estimated using the χ^2 test, the Student's *t* test, and the log–rank test (29). Multivariate analysis was performed using the Cox regression model (30). A probability level of 0.05 was chosen for statistical significance. The Radiotherapy Oncology Group (RTOG) late toxicity scales were used to assess the late morbidity (31).

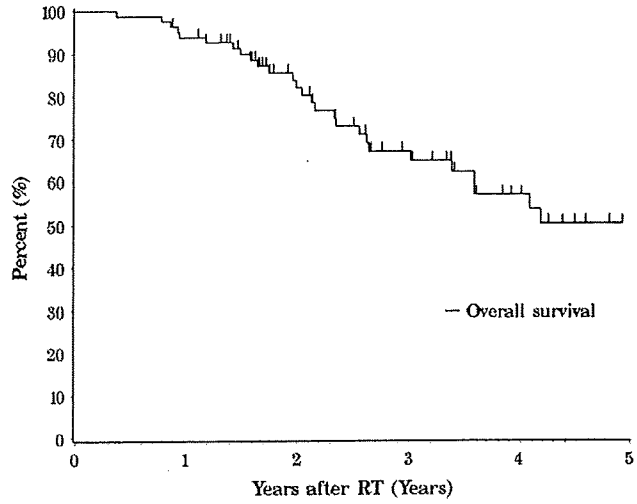

Fig. 1. Actuarial overall survival curves for 84 patients with clinically localized hormone-refractory prostate cancer treated with radiotherapy (RT).

RESULTS

Of 84 patients, 27 (32%) died during the period of this analysis. Of these 27 patients, 24 died of prostate cancer, and the remaining 3 died without any sign of clinical recurrence (2 died of intercurrent disease, 1 died of unknown cause). The 3-year actuarial overall survival rate for all 84 patients was 67% (Fig. 1). With regard to the site of recurrence, 37 patients had clinical failure (local only in 3 patients, local with regional in 1 patient, local with distant metastases in 1 patient, regional in 3 patients, distant metastases in 24 patients, and regional and distant metastases in 5 patients). The 3-year actuarial PFS and local control rates in all 84 patients after radiotherapy were 61% and 93%, respectively (Fig. 2). Although distant metastases and/or regional lymph node metastases were seen in 34 patients (40%), local progression was observed in only 5 patients (6%), including 2 patients with simultaneous regional/distant metastases. The total dose and radiation field treated were tested for correlation with local control (Table 3). Ten of 12 patients (83%) treated with <60 Gy achieved local control, whereas 54 of 55 patients (98%) treated with ≥66 Gy achieved local control ($p = 0.024$). Thirty-three of 34 patients (97%) treated with whole-pelvis irradiation with boost and 46 of 50 patients (92%) treated with local-field irradiation achieved local control; this difference was not statistically significant ($p = 0.34$). Table 4 indicates regional control according to N stage and radiation field. Twenty-eight of 34 patients (82%) treated

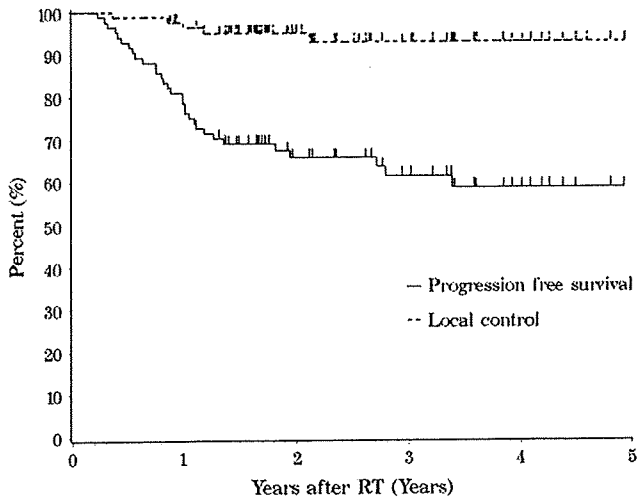

Fig. 2. Actuarial progression-free survival and local control curves for 84 patients with clinically localized hormone-refractory prostate cancer treated with radiotherapy (RT).

with whole-pelvis irradiation with boost and 47 of 50 patients (94%) treated with local-field irradiation achieved regional control; this difference was not statistically significant (p = 0.09).

Of all 84 patients, the median nPSA12 in patients with clinical failure after radiotherapy and in those without clinical failure was 3.10 ng/mL (range, 0.36–1400 ng/mL) and 0.50 ng/mL (range, 0–50.39 ng/mL), respectively. Figure 3 shows the distribution of nPSA12 according to the achievement of clinical control. More than half of patients with clinical control (27 of 52 patients, 52%) had nPSA12 of <0.5 ng/mL, whereas only 1 of 32 patients (3%) with clinical failure had nPSA of <0.5 ng/mL ($p < 0.0001$). For the 27 patients who achieved an nPSA12 <0.5 ng/mL and who did not experience clinical failure, the median time from the completion of radiotherapy to achievement of nPSA12 <0.5 ng/mL was 6.4 months (range, 0.07–11.7 months).

In the present study, patients with nPSA12 <0.5 ng/mL were assigned to the low nPSA12 group (n = 28), whereas those with nPSA12 ≥0.5 ng/mL were assigned to the high nPSA12 group (n = 56). The 3-year actuarial PFS rate in patients with high nPSA12 and in patients with low nPSA12 was 96.4% and 43.9%, respectively (Fig. 4). The difference between these two groups was statistically significant ($p <$ 0.0001). In a univariate analysis, nPSA12 and pretreatment PSA value had a statistically significant impact on PFS (Table 5). No significant differences in PFS were seen with respect to other factors. In a multivariate analysis, nPSA12 alone was a significant prognostic factor for PFS (Table 6).

Table 3. Local control according to radiation dose and field

			Incidence of LC	
Total dose (Gy)	n	Patients with LC	WP + B	Local
<60	12	10 (83)	5/5	5/7
60–<62	15	15 (100)	10/10	5/5
62–<64	2	0	0	0/2
64–<66	2	2	1/1	1/1
66–<68	17	16 (94)	7/8	9/9
68–<70	14	14 (100)	2/2	12/12
≥70	22	22 (100)	8/8	14/14
Total	84	79 (94)	33/34 (97)	46/50 (92)

Abbreviations: LC = local control; WP = whole pelvis; B = boost.
Values in parentheses are percentages.

Table 4. Regional control according to N stage and radiation field

			Incidence of LC	
N stage	n	Patients with LC	WP + B	Local
N0	74	68 (92)	23/26	45/48
N1	10	7 (70)	5/8	2/2
Total	84	75 (89)	28/34 (82)	47/50 (94)

Abbreviations as in Table 3.
Values in parentheses are percentages.

Late morbidity of RTOG Grade 2–3 was observed in 11 patients (13%). A total of 8 patients experienced late rectal toxicity, 3 patients had late urinary toxicity, and 1 patient had multiple late rectal and urinary toxicities (Grade 3 rectal stricture, Grade 2 incontinence, and Grade 2 urethral stricture). There were no cases of Grade 4 toxicity (Table 7). Regarding 7 patients who had Grade 3 late complications, CT-based treatment planning was done in only 1 patient (14%), and conformal therapy was supplemented in 2 patients (29%).

DISCUSSION

The present study indicated that external beam radiotherapy had an excellent local control rate for clinically localized hormone-refractory prostate cancer. Several reports have also indicated that radical radiotherapy had an excellent local control rate for these tumors (20, 32). Akimoto *et al.* (32) treated

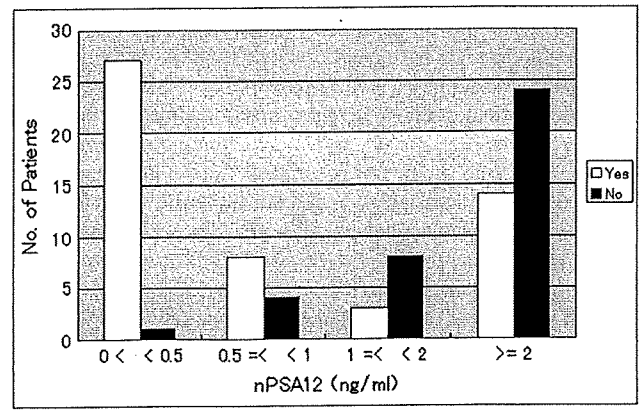

Fig. 3. Distribution of nPSA12 according to clinical control. More than half of patients with clinical control had a prostate-specific antigen nadir at 12 months (nPSA12) <0.5 ng/mL, whereas only 1 of 32 patients who experienced clinical failure had an nPSA12 <0.5 ng/mL.

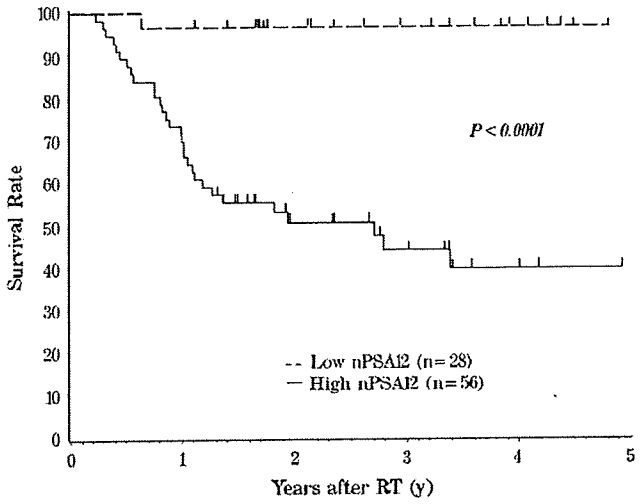

Fig. 4. Actuarial progression-free survival (PFS) curves according to the level of prostate-specific antigen nadir at 12 months (nPSA12). There were significant differences in PFS between patients with a low nPSA12 (<0.5 ng/mL) and those with a high nPSA12 (≥0.5 ng/mL).

53 patients with localized hormone-refractory prostate cancer with external beam radiotherapy, and only 2 patients (4%) had local failure as the first site of recurrence (32). Similarly, our initial report indicated that local progression was observed in only 1.6% of patients with hormone-refractory prostate cancer when treated with radiotherapy (20). In the present study, only 5 of 84 patients (6%) developed local failure after radiotherapy. These results indicate that external beam radiotherapy is effective in preventing local recurrence of these tumors.

Although the dose–response relationship in patients who undergo irradiation for localized hormone-refractory prostate cancer has not yet been clearly established, higher doses with curative intent can result in fairly prolonged survival in some patients. Furuya *et al.* (8) treated 11 patients with local progression by external radiotherapy at a dose of 50–66.6 Gy, and no patients suffered from local progression. Lankford *et al.* (9) examined 29 patients with localized hormone-refractory prostate cancer treated with radiotherapy and showed that the 3-year local control rate after irradiation of >60 Gy was 90%, compared with only 29% for those receiving ≤60 Gy. In the present study, the 3-year local control in 84 patients treated with a median dose of 66 Gy was 93%, and 52 of 53 patients (98%) treated with ≥66 Gy achieved local control. Therefore, radiation doses of ≥66 Gy seem to be appropriate for localized hormone-refractory prostate cancer patients when treated with external beam radiotherapy. However, it is important to note that in the present study almost all patients who had Grade 3 late complications were treated without CT-based treatment planning and/or conformal therapy. Therefore, CT-based treatment planning and/or conformal therapy should be required to reduce late complications. Concerning radiation field, we did not find significant differences in both local and regional control between patients treated with whole-pelvis irradiation with boost and localized field only. Therefore, localized filed irradiation may be sufficient in this patient population. Further studies are required to determine whether localized field irradiation can be sufficient for these patients.

Table 5. Univariate analysis of various potential prognostic factors for PFS in patients with hormone-refractory prostate cancer treated with external beam radiotherapy

		Univariate analysis	
Variable	*n*	3-y PFS (%)	*p*
nPSA12 (ng/mL)			0.0029*
<0.5	28	96	
≥0.5	56	44	
Pretreatment PSA (ng/mL)			0.0260*
<20	14	93	
≥20	45	47	
N stage			0.0737
N0	58	67	
N1	10	50	
Preradiotherapy PSA (ng/mL)			0.0997
<4	14	86	
≥4	69	57	
Age (y)			0.1102
<75	51	54	
≥75	33	74	
Differentiation			0.1398
Well/moderately	38	51	
Poor	31	70	
KPS (%)			0.4603
≤80	45	60	
>80	35	62	
Pelvic irradiation			0.6006
Yes	34	60	
No	50	63	
T stage			0.6886
T0–2	18	60	
T3–4	66	63	
Total radiation dose (Gy)			0.6939
<60	12	53	
≥60	72	62	
Use of chemotherapy			0.7089
Yes	23	64	
No	58	62	
Gleason combined score			0.9972
≤6	5	100	
>6	13	69	

Abbreviation: PFS = progression-free survival; nPSA12 = prostate-specific antigen nadir within 12 months. Other abbreviations as in Table 1.

* $p < 0.05$.

The present study also indicated that patients with a high nPSA12 had a significantly lower PFS rate than patients with a low nPSA12. Moreover, nPSA12 was an independent prognostic factor for PFS in patients with localized hormone-refractory prostate cancer treated with radiotherapy. To our knowledge, this is the first report to demonstrate the utility of nPSA12 in determining prognosis in patients with localized hormone-refractory prostate cancer treated with radiotherapy. Concerning previously untreated prostate cancer, Alcabtare *et al.* (10) indicate that nPSA12 is independent of radiation dose, T stage, Gleason score, pretreatment initial

Table 6. Multivariate analysis of potential prognostic factors for PFS in patients with hormone-refractory prostate cancer treated with external beam radiotherapy

Variable	RR (95% CI)	*p*
nPSA12 (<0.5 vs. ≥0.5 ng/mL)	10.965 (1.454–82.671)	0.0202*
Pretreatment PSA (<5 vs. ≥5 ng/mL)	6.489 (0.854–49.430)	0.0706

Abbreviations: RR = relative risk; CI = confidence interval. Other abbreviations as in Tables 1 and 5.

* $p < 0.05$.

Table 7. Late complications ($n = 84$)

Complication	Toxicity grade 2	3	4	Total dose (Gy) (Grade 3)
Rectal				
Bleeding	3	5	0	60–71*
Stricture	0	1	0	66
Urinary				
Incontinence	1	0	0	
Stricture	2	1	0	50

* Median total dose, 70 Gy.

PSA value, age, and PSA doubling time, and dichotomized nPSA12 (≤2 vs. >2 ng/mL) was independently related to distant metastases and cause-specific mortality. Ray *et al.* (11) indicated that patients with nPSA12 ≤2.0 ng/mL had significantly higher 8-year PSA failure-free survival and overall survival rates than patients with nPSA12 >2.0 ng/mL, and nPSA12 was an independent prognostic factor for prostate cancer patients treated with radiotherapy alone. These results suggest that nPSA12 may be a useful marker for localized hormone-refractory prostate cancer patients treated with radiotherapy, as well as for patients with previously untreated prostate cancer treated with radiotherapy. Because nearly all of the patients in the present study achieved local control, nPSA12 levels may largely reflect the recurrence risk for both regional and distant metastases.

Several previous studies have suggested other potential factors associated with the risk of prostate cancer recurrence, such as preradiotherapy PSA value, PSA doubling time, and Gleason score (9, 32, 33). Our results indicated that pretreatment PSA value has a significant impact on PFS, although multivariate analyses failed to confirm the significance (Table 4). Further studies are required to evaluate the influence of additional factors, such as pretreatment PSA value, on clinical outcomes for localized hormone-refractory patients treated with radiotherapy.

Patients with hormone-refractory prostate cancer generally have poor prognoses, even if the disease is regionally localized. The most common cause of failure in patients treated with radiotherapy is distant metastases (9, 20, 32). Akimoto *et al.* (32) indicated that 15 of 53 patients (28%) showed locoregional and/or distant metastases; the sites of the first recurrence were bone metastasis in 10, lymph node in 3, and local failure in 2 patients (32). Lankford *et al.* (9) demonstrated that there were 6 local and 14 regional or distant failures after locoregional radiotherapy in 29 patients with localized hormone-refractory prostate cancer, with a 4-year survival rate of 39%. In the present study, 34 of 84 patients (40%) developed distant metastases with or without local/regional recurrence after radiotherapy. Therefore, new treatment approaches for preventing distant metastases should be explored. Recently, a survival benefit of treatment with docetaxel-containing chemotherapy for patients with advanced prostate cancer was demonstrated in two large Phase III clinical trials (34, 35). Therefore, optimal adjuvant chemotherapy combined with radiotherapy may be a treatment of choice for high-risk patients.

In conclusion, our results indicated that external beam radiotherapy had an excellent local control rate for localized hormone-refractory prostate cancer and should be considered the treatment of choice for these tumors. Our results also indicate that nPSA12 is an early predictor of clinical failure that is independent of radiotherapy dose and other determinants of outcome after radiotherapy for patients with localized hormone-refractory prostate cancer. Because the majority of clinical failures are distant metastases, nPSA12 could potentially help identify patients at high risk who might benefit from earlier application of adjuvant systemic therapy. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

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Patterns of Radiation Treatment Planning for Localized Prostate Cancer in Japan: 2003–05 Patterns of Care Study Report

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Objective: The purpose of this study is to identify the treatment planning process for Japanese patients with localized prostate cancer.
Methods: The Patterns of Care Study conducted a random survey of 61 institutions nationwide. Detailed information was collected on prostate cancer patients without distant metastases who were irradiated during the periods 2003–05. Radiation treatment planning and delivery were evaluated in 397 patients who were treated radically with external photon beam radiotherapy.
Results: Computed tomography data were used for planning in ~90% of the patients. Contrast was rarely used for treatment planning. Simulations and treatments were performed in the supine position in almost all patients. Immobilization devices were used in only 15% of the patients. Verification of the treatment fields using portal films or electric portal imaging devices was performed in most of the patients. However, regular or multiple verifications in addition to initial treatment and/or portal volume changes were performed in only 30% of the patients. Typical beam arrangements for treatment of the prostate consisted of a four-field box. Three-dimensional conformal techniques were applied less frequently in non-academic hospitals than in academic ones. Modernized multileaf collimators with leaf widths $\leq$10 mm were used in about two-thirds of the patients. Although the total doses given to the prostate were affected by the leaf widths, there were no significant differences between leaf widths of 5 and 10 mm.
Conclusions: The results of the survey identified certain patterns in the current treatment planning and delivery processes for localized prostate cancer in Japan.

Key words: prostate cancer – treatment planning – Patterns of Care Study

INTRODUCTION

Recent years have seen rapid modernization in the development of new radiotherapy equipments and techniques, and great growth in their availability in Japan. Accordingly, radical radiotherapy has been accepted as an option for the curative treatment of prostate cancer (1,2), and a number of patients with prostate cancer have been treated with not only three-dimensional conformal radiotherapy (3DCRT), but also with intensity-modulated radiotherapy (IMRT). However, as with any newly arrived medical technology, the treatment planning process and methods are critical factors to affect the treatment results. Therefore, it was deemed very important to examine the structures and processes of treatment planning and delivery for localized prostate cancer in Japan.

The Japanese Patterns of Care Study (PCS) national survey is a retrospective study designed to investigate the

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national practice processes of radiotherapy for selected malignancies over certain periods of time (3). In the PCS survey, detailed information about the structures, processes and outcomes of radiation treatment was collected. The 2003–05 PCS, which is the most recent PCS, included questionnaires designed to assess treatment planning practices currently in use. The goal of this current report is to identify the treatment planning process for patients with localized prostate cancer in Japan.

PATIENTS AND METHODS

The methods used in data collection for the PCS have been described previously (1–3). From a stratified Facilities Master List, 34 hospitals were randomly selected from A institutions (university hospitals/cancer centers) and 27 hospitals from B institutions (non-academic hospitals) (Table 1). Between August 2006 and September 2008, each of the chosen facilities was visited by member physicians of the PCS group. A total of up to 10 medical records from each institution were randomly selected and reviewed. The following eligibility criteria were used in the process survey. The patients were required to have been diagnosed with adenocarcinoma of the prostate without evidence of distant metastases; they had to have been treated with radiotherapy between 2003 and 2005; and the patients must not have been diagnosed with any other malignancy nor have been previously treated with radiotherapy. From a total of 592 eligible cases (Table 1), 397 patients were evaluated who had been treated radically with external photon beam radiotherapy. Patients who were treated after surgery or after progression from hormonal therapy were excluded.

In this paper, we focused on the patterns of radiation treatment planning and delivery for localized prostate cancer. The data were stratified according to whether the treatment took place in academic or non-academic facilities, and compared on this basis. For statistical analysis, the differences between proportions were tested by the χ^2 test. A P value <0.05 was considered to indicate a statistically significant difference.

Table 1. The number of patients examined in this analysis

	No. of facilities	No. of total prostate patients	No. of patients in this study
A institutions (university hospitals and cancer centers)			
A1 (≥410 patients per year)	17	180	111
A2 (<410 patients per year)	17	164	105
B institutions (non-academic hospitals)			
B1 (≥130 patients per year)	15	148	117
B2 (<130 patients per year)	12	100	64
Total	61	592	397

RESULTS

Treatment Planning and Implementation

The computed tomography (CT) simulation usage rates are shown in Table 2. CT data were used for planning in ~90% of the patients. The majority of the CT data were obtained from dedicated CT scanners in A institutions, but almost half of the CT data were obtained from diagnostic CT scanners in B institutions. X-ray simulation was used more frequently in B institutions. Contrast was rarely used for treatment planning.

Verification of the treatment fields using portal films or electric portal imaging devices was undertaken in most of the patients. However, regular or multiple verifications in addition to initial treatment and/or portal volume changes were performed in only 30% of the patients.

Position and Immobilization of Patients

Simulations and treatments were performed in the supine position in almost all patients (Table 3). Immobilization devices were used for only 15% of the patients.

Treatment Techniques

Treatment techniques are shown in Table 4. The most commonly used photon energy was 10 MV. In B institutions, lower energies <10 MV were used more frequently.

Table 2. Treatment planning and implementation

	Stratification[a]		P value
	A	B	
Simulation			0.021
CT simulation with/without X-ray simulation	203 (94.0%)	158 (87.3%)	
Dedicated CT	171 (79.2%)	82 (45.3%)	
Diagnostic CT	32 (14.8%)	76 (42.0%)	
X-ray simulation only	13 (6.0%)	23 (12.7%)	
Contrast used for treatment planning			0.871
None	213 (98.6%)	179 (98.9%)	
Rectal barium	0	2 (1.1%)	
Urethrogram	1 (0.5%)	0	
Both	1 (0.5%)	0	
Portal verification			0.031
None	9 (4.2%)	0	
Initial treatment or field change only	147 (68.1%)	128 (70.7%)	
Regular or multiple intervals	60 (27.8%)	53 (29.3%)	

CT, computed tomography.
[a]Because some data were missing, the total numbers of patients may be less than the actual numbers.

Table 3. Position and immobilization of patients

	Stratification		*P* value
	A	B	
Position			0.403
Supine	216 (100%)	179 (98.9%)	
Prone	0	2 (1.1%)	
Immobilization			0.434
None	174 (80.6%)	158 (87.3%)	
Cast[a]	24 (11.1%)	14 (7.7%)	
Body frame[b]	9 (4.2%)	9 (5.0%)	
Others/unknown	9 (4.2%)	0	

[a]'Cast' was defined as a firm body support system, such as vacuum pillows.
[b]'Body frame' was defined as an immobilized system, such as a system using a base plate and body shells.

The typical beam arrangement for treatment of the prostate consisted of a four-field box. Treatment plan included a moving field in one-third of the patients. 3D conformal techniques including IMRT were generally applied less frequently in B institutions than in A institutions (A1, 97.3%; A2, 53.3%; B1, 59.8%; and B2, 37.5%). Modernized multileaf collimators (MLC) with leaf widths $\leq$10 mm were used in about two-thirds of the patients.

Total Dose

The median dose given to the prostate was 70 Gy (A1, 70 Gy; A2, 70 Gy; B1, 67.8 Gy; and B2, 66 Gy). Figure 1 shows the distributions of doses delivered to the prostate according to the leaf width of MLC. Although the doses were affected by the leaf width, there were no significant differences between the dosages delivered at 5 mm and those delivered at 10 mm MLC leaf width ($P = 0.12$).

DISCUSSION

This is the first detailed survey report focusing on the radiation treatment planning for prostate cancer in Japan. This report provides a clear picture of the present practices relating to treatment planning in this country. Because few reports exist on treatment planning practices for prostate cancer (4,5), these data will serve as a baseline for future surveys as well as for the multicenter trials including radiotherapy.

The results in this study show that contrast was rarely used for treatment planning in Japan. In the 1989 US PCS (4), contrast was used in the bladder and rectum in 25% and 34% of the patients, respectively. However, only 51% of the patients had CT data for planning in the 1989 PCS (4). It is recommended that rectal or bladder dye should be utilized to

Table 4. Treatment techniques

	Stratification		*P* value
	A	B	
Energy (MV)			0.0000
4–5.9	10 (4.8%)	13 (7.4%)	
6–9.9	8 (3.9%)	42 (24.0%)	
10–14.9	149 (72%)	113 (64.4%)	
$\geq$15	40 (19.3%)	7 (4.0%)	
Field arrangement for the prostate			0.0000
2-field	36 (16.8%)	15 (8.4%)	
3-field	7 (3.3%)	2 (1.1%)	
4-field	49 (22.9%)	71 (39.7%)	
5-field	33 (15.4%)	4 (2.2%)	
$\geq$6-field	26 (12.2%)	12 (6.7%)	
Rotational	21 (9.8%)	16 (8.9%)	
Pendulum	41 (19.2%)	54 (30.2%)	
3DCRT/IMRT technique			0.0000
3DCRT-dynamic	64 (29.6%)	54 (29.8%)	
3DCRT-static	87 (40.3%)	38 (21.0%)	
IMRT-step and shoot	13 (6.0%)	2 (1.1%)	
IMRT-sliding window	0	0	
None	52 (24.1%)	87 (48.1%)	
Width of multileaf collimator leaves			0.0000
5 mm	38 (17.6%)	53 (29.3%)	
10 mm	120 (55.6%)	52 (28.7%)	
20 mm	10 (4.6%)	19 (10.5%)	
Block	15 (7.0%)	31 (17.1%)	
None	26 (12.0%)	26 (14.4%)	
Unknown	7 (3.2%)	0	

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

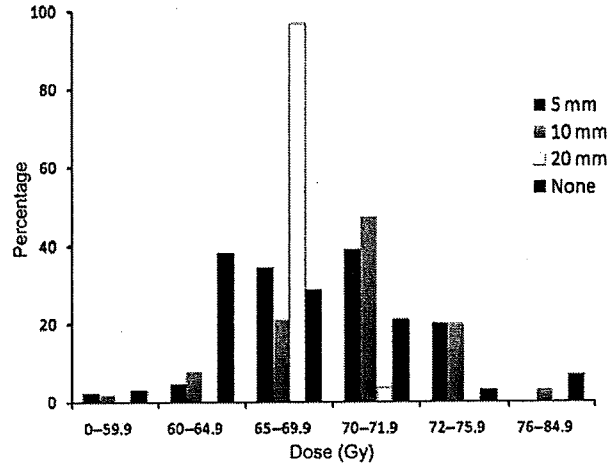

Figure 1. Distribution of radiation doses delivered to the prostate according to the leaf widths of multileaf collimators.

help design field blocking and beam arrangements, if X-ray simulation is used (4,6). However, contrast may not be needed to determine the position of the prostate when CT simulation is performed. In this survey, there were no questionnaires on the usage of magnetic resonance imaging (MRI) images for prostate cancer treatment planning. Going forward, it is expected that MRI/CT image fusion techniques will be increasingly important to define the anatomical structures including the prostate (7,8). The next PCS survey will take this issue into consideration.

Regular or multiple verifications of the treatment fields were performed in only 30% of the patients in this study. In the USA, radiation fields were verified with regular intervals in 60% of the prostate patients surveyed in the 1989 PCS (4). It is hoped that if electric portal imaging devices become more popular in Japan, verification of the treatment fields will be performed more frequently.

Simulations and treatments were performed in the supine position in almost all patients. Published literature suggests a variation in results between the use of the prone and supine positions for prostate cancer radiotherapy. Several authors demonstrated that the rectal dose was reduced in the prone position (9,10). However, in the absence of immobilization devices, daily setup reproducibility may be less accurate for the prone position, primarily due to systematic setup variations (10). Patient positioning procedures in prostate radiotherapy should be evaluated in each institution, in particular if the radiation doses to the prostate are high.

Immobilization was used in only 15% of the patients. This may be in part because immobilization devices for body malignancies are not covered by health insurance in Japan. As mentioned above, patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (11). More widespread use of immobilization devices will also be required with an increase in treatment using 3DCRT or IMRT, which utilize higher dosages of radiation.

The radiation doses delivered to the prostate were affected by the leaf width of MLC. However, there were no significant differences between a 5 mm and a 10 mm MLC leaf size. Leal et al. (12) showed that the impact on the clinical dose distribution due to the MLC leaf width change from 10 to 5 mm is quite low on the dose distribution in patients treated with 3DCRT and IMRT. On the other hand, Wang et al. (13) insisted that the use of the micro-MLC for IMRT of the prostate resulted in significant improvement in the dose distributions to the prostate and critical organs. Although narrower leaves give better sparing of organs at risks, the clinical value should be carefully evaluated.

Several significant variances in the process according to the stratification of institutions were also observed. Although CT data were used for planning in ~90% of the patients, 3D conformal techniques including IMRT were applied less frequently in B institutions. In particular, only 37.5% of the patients were treated with 3D conformal techniques in B2 institutions. In B institutions, lower photon energies <10 MV were also used more frequently. Delivery of high radiation doses without the use of 3D conformal techniques may produce late morbidity of the surrounding tissues. Because some guidelines have recommended that 3DCRT or IMRT techniques should be employed in external beam radiotherapy for prostate cancer (14,15), structural improvement in B institutions should be urgently considered.

In conclusion, the results of the survey identified the standard of practice for treatment planning of prostate cancer in Japan. Although the preferred methods of planning and delivery have been defined somewhat differently at various institutions, it is necessary to define and develop recommended guidelines for the treatment planning process, in particular, for a clinical trial on radiotherapy for prostate cancer.

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Conflict of interest statement

None declared.

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