practice patterns of post-operative radiotherapy during 1995–1997 have already been published elsewhere (3). The purpose of this study is to establish national patterns of practice for uterine cervical cancer patients who received radiation therapy without planned surgical treatments during the period 1995–1997. The influence of institutional stratification on process of care was also analyzed.

PATIENTS AND METHODS

The JPCS conducted a national survey of patients with uterine cervical cancer treated with radiotherapy during 1995–1997. The survey was performed from September 1998 to March 2001. The JPCS developed an original data format for patients with uterine cervical cancer with reference to the fifth PCS format of the American College of Radiology (ACR). Seventy-three out of 556 institutions were selected for the survey by using a stratified two-staged cluster sampling method. The data collection method consisted of two steps of random sampling. Prior to the random sampling, all the institutions were classified into four groups. The criteria for stratification of the institutions have been described elsewhere (2,3). Briefly, institutional stratification of JPCS was as follows: A1, academic institutions treating ≥300 patients a year; A2, academic institutions treating <300 patients a year; B1, non-academic institutions treating ≥120 patients a year; and B2, non-academic institutions treating <120 patients a year. Academic institutions include cancer center hospitals and university hospitals. Non-academic institutions consist of other facilities such as national, prefectural, municipal and private hospitals.

The first step was to randomly select institutions from each group. The second step was to randomly select eligible patients from each of the sampled institutions. To be eligible for this study, patients had to meet several criteria: carcinoma, treated from 1995 to 1997, without distant metastases, without prior or concurrent malignancies, without gross para-aortic lymph node metastases and no previous pelvic radiotherapy. The JPCS surveyors consisted of 20 radiation oncologists from 10 academic institutions. One radiation oncologist visited and surveyed the data by reviewing patients' charts for each of the institutions. Data collection included patient characteristics (e.g. patient history, age, performance status, laboratory data, pathology, staging), extent of work-up for lymph node status, details of treatment (e.g. radiotherapy, chemotherapy, surgery) and treatment outcomes. The JPCS collected clinical data on 1065 patients with uterine cervical cancer who were treated with radiotherapy. In this study, 591 patients treated by radiotherapy without planned surgery were analyzed. These include 207 patients from A1 institutions, 145 patients from A2 institutions, 179 patients from B1 institutions and 60 patients from B2 institutions.

Statistical significance was tested by the χ^2 test. Cases with unknown values were included, but cases with missing values were not included in calculations of percentage and significance.

RESULTS

Patients and Tumor Characteristics (Table 1)

Data on height and weight were collected in 384 (65%) and 429 (73%) patients, respectively. The median height was 150 cm (range 119–168) whilst the median weight was 50 kg (range 26–97). Age data were collected for all 591 patients. Seventy-four patients (13%) were younger than 50 years, and 194 patients (33%) were older than 74 years. Patients over 74 years were frequently seen in A2 (37%) and B2 (50%) compared with in A1 (28%) and B1 (29%) institutions. The Karnofsky performance status (KPS) was 90–100 in 37%, and was <80 in 23%. The KPS distribution varied significantly by the institution strata ($P = 0.002$). Although approximately half of the patients in the A1 stratum had a favorable KPS (90–100), this was only the case for 20% of B2 institutions. Data on the pre-treatment hemoglobin value were obtained for 489 cases (83%). There was a significant difference in hemoglobin value among the groups of institutions ($P < 0.0001$). Patients of A1 and B1 institutions had higher hemoglobin values than those of A2 and B2 institutions. Most patients (95%) had histology of squamous cell carcinoma. No significant difference in histology was observed among each stratum. Patients with stage III were seen most frequently. Information of hydronephrosis/non-functioning kidney was noted for 267 of 280 stage III patients (95%), and 72 of 75 stage IVA patients (96%). Sixty patients (22%) with stage III and 41 patients (57%) with stage IVA had hydronephrosis/non-functioning kidney. Institutional strata did not significantly affect this distribution.

For the assessment of pelvic nodal status, lymphangiography (four out of 495 patients; 1%) and surgical exploration (17 out of 505 patients; 3%) were rarely performed. Data on the nodal status were recorded using computed tomography (CT) in 369 out of 547 patients (67%) and magnetic resonance imaging (MRI) in 320 out of 540 patients (59%). However, data with an 'unknown' value were frequent for these items (CT, 146; MRI, 128). There was no significant difference among each institutional stratum for these variables on pelvic nodal evaluation.

Treatment

Only 12 (2%) of 519 patients for whom information was available entered an investigational protocol.

External beam radiotherapy

Treatment parameters of external beam radiotherapy (EBRT) according to the stratified institutions are listed in Table 2. Photon beams of 10–14 MV were the most popular category used for EBRT. Beam energies utilized varied significantly by institution strata ($P < 0.0001$). A beam energy of ≥10 MV was used for 93% in A1, 68% in A2, 55% in B1 and 18% in B2. For most patients, EBRT was given in daily fraction doses of 1.8 or 2.0 Gy. Treatment volume included only the pelvic region for almost all patients. Extended field prophylactic radiotherapy including the para-aortic region was rarely performed. The

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions				*P*-value	Total
	A1	A2	B1	B2		
No. of patients	207	145	179	60		591
Age, years						
Range	28–91	33–90	33–94	33–94		28–94
Median	69	71	69	75		70
KPS					0.002	
≤70	35 (17%)	42 (29%)	39 (22%)	17 (28%)		133 (23%)
80	68 (34%)	51 (36%)	82 (46%)	31 (52%)		232 (40%)
90	83 (41%)	39 (28%)	55 (31%)	12 (20%)		189 (32%)
100	16 (8%)	10 (7%)	2	0		28 (5%)
Missing	5	3	1	0		9
Hemoglobin (g/dl)					<0.0001	
<10	39 (21%)	39 (29%)	46 (26%)	23 (38%)		147 (26%)
10–12	61 (33%)	49 (36%)	54 (31%)	24 (40%)		188 (34%)
>12	67 (36%)	28 (20%)	51 (29%)	8 (14%)		154 (28%)
Unknown	17 (9%)	21 (15%)	25 (14%)	5 (8%)		68 (12%)
Missing	23	8	3	0		34
Histology					0.244	
Squamous cell carcinoma	188 (92%)	137 (95%)	173 (98%)	56 (95%)		554 (95%)
Adenocarcinoma	14 (7%)	4 (3%)	3	2		23 (4%)
Adenosquamous cell carcinoma	1	2	0	1		4
Other	2	1	1	0		4
Missing	2	1	2	1		6
FIGO stage					0.01	
I	9 (4%)	26 (18%)	16 (9%)	6 (10%)		57 (10%)
II	62 (30%)	38 (27%)	56 (32%)	15 (25%)		171 (29%)
III	115 (56%)	57 (40%)	75 (42%)	33 (55%)		280 (48%)
IVA	17 (8%)	22 (15%)	30 (17%)	6 (10%)		75 (13%)
Other (CIS, IVB)	4 (2%)	0	1	0		5
Missing	0	2	1	0		3

majority of the patients were treated with anterior and posterior opposed fields. The four-box technique was rarely used. Approximately 70% of the patients had a midline block (MLB) for a portion of their treatment course. Use of an MLB varied significantly among each stratum ($P < 0.0001$). An MLB was used more frequently in A1 compared with other strata.

Brachytherapy

Only one patient (B2 institution) was treated with interstitial brachytherapy. Table 3 shows details of intracavitary brachytherapy (ICBT). ICBT was performed for approximately three-quarters of patients. Institution strata correlated significantly with the application of ICBT. ICBT was administered to 85% of patients in A1, 78% in A2, 75% in B1 and 53% in B2 ($P < 0.0001$). Performance of ICBT correlated well with the use of an MLB for EBRT. However, a discrepancy was observed between these two in A2 institutions. Further analysis of MLB utilization for patients treated with ICBT revealed that the MLB utilization rate was lower in A2 (74%) than other strata (A1, 93%; B1, 92%; B2, 88%). Use of ICBT according to the FIGO stage was noted for 584 patients. Forty-three patients with stage I received ICBT (75%), 144 patients with stage II (85%), 220 patients with stage III (79%) and 42 patients with stage IVA (55%). The majority of patients were treated with high-dose-rate (HDR) ICBT. Low-dose-rate (LDR) was used slightly more frequently in A1 institutions (14%) compared with other strata (2–7%). The most popular radionuclide used for brachytherapy sources was cobalt-60 (Co-60), followed by

Table 2. Treatment parameters of external beam radiotherapy

Parameters	Stratification of institutions				*P*-value	Total
	A1	A2	B1	B2		
Beam energy					<0.0001	
Co-60	1	7 (5%)	0	9 (15%)		17 (3%)
3–5 MV	1	23 (16%)	44 (25%)	11 (18%)		79 (14%)
6–9 MV	12 (6%)	6 (4%)	35 (20%)	29 (48%)		82 (14%)
10–14 MV	145 (74%)	87 (62%)	95 (55%)	11 (18%)		338 (59%)
≥15 MV	37 (19%)	8 (6%)	0	0		45 (8%)
Other/unknown	1	9 (7%)	0	0		10 (2%)
Missing	10	5	5	0		20
Treatment volume					NS	
Pelvis only	197 (97%)	138 (98%)	170 (98%)	60 (100%)		571 (98%)
Pelvis + PAN	5	3	2	0		5
Other	1	0	2	0		2
Missing	4	4	5	0		13
Technique					NS	
AP–PA	195 (99%)	136 (96%)	169 (97%)	60 (100%)		560 (98%)
4-field box	2	4 (3%)	5 (3%)	0		11 (2%)
Other	0	1	0	0		1
Missing	10	4	5	0		19
Midline block					<0.0001	
Yes	156 (81%)	82 (59%)	120 (71%)	28 (47%)		386 (69%)
No	36 (19%)	56 (40%)	47 (28%)	32 (53%)		171 (30%)
Unknown	1	2	1	0		4
Missing	14	5	11	0		30
Daily fraction size					0.0094	
<180 cGy	2 (1%)	8 (6%)	2 (1%)	1 (1%)		13 (2%)
180 cGy	74 (37%)	72 (51%)	85 (49%)	28 (47%)		259 (45%)
181–199 cGy	0	0	0	0		0
200 cGy	124 (61%)	58 (41%)	86 (50%)	31 (52%)		299 (52%)
>200 cGy	1	2 (1%)	0	0		3
Unknown	1	1	0	0		2
Missing	5	4	6	0		15

PAN, para-aortic lymph nodes.

iridium-192 (Ir-192). Ir-192 was used more frequently in A1 institutions than in A2 and B1. Adequate sedation was rarely performed at the time of ICBT applicator insertion. Over half of the patients were treated without any sedation. Patients in B1 institutions tended to be treated more with sedation than other institution strata. The most frequently used method was the use of non-steriodal anti-inflammatory drugs (NSAIDs) delivered orally or rectally in all strata. ICBT was done using various methods. A combination of tandem and ovoid applicator was most frequently used regardless of institution strata.

Radiation dose and treatment duration

For the following analyses regarding dose of ICBT, 361 patients (HDR, 327 patients; LDR, 34 patients) treated with a combination of tandem and vaginal applicator or tandem only were analyzed. Total dosage of radiotherapy in 327 patients treated with HDR-ICBT according to the institution strata is shown in Table 4. The median single point A dose of ICBT was 600 cGy for HDR, and 1412 cGy for LDR. The most frequent category of single dose of HDR-ICBT was 600–699 cGy, followed by 500–599 and 700–799 cGy.

Table 3. Details of intracavitary brachytherapy (ICBT)

Parameters	Stratification of institutions				*P*-value	Total
	A1	A2	B1	B2		
ICBT					<0.0001	
Yes	177 (85%)	111 (78%)	134 (75%)	32 (53%)		454 (77%)
No	30 (15%)	32 (22%)	42 (24%)	28 (47%)		132 (23%)
Unknown/other	0	0	3	0		3
Missing	0	2	0	0		2
Dose rate					0.011	
HDR	147 (84%)	104 (98%)	107 (88%)	28 (90%)		386 (89%)
LDR	25 (14%)	2 (2%)	9 (7%)	1 (3%)		37 (9%)
MDR	1	0	1	0		2
Mix*	1	0	1	0		2
N/A	1	0	3 (3%)	2 (7%)		6 (1%)
Missing	2	5	13	1		21
Source					0.0001	
Co-60	80 (46%)	83 (78%)	89 (67%)	17 (55%)		269 (60%)
Ir-192	69 (39%)	19 (18%)	12 (9%)	13 (42%)		113 (25%)
Cs-137	27 (15%)	4 (4%)	1	1 (3%)		33 (7%)
Ra-226	0	0	9 (7%)	0		9 (2%)
Unknown	0	1	21 (16%)	0		22 (5%)
Missing	1	4	2	1		8
Sedation					<0.0001	
None	100 (61%)	56 (62%)	30 (26%)	13 (57%)		199 (51%)
General/spinal anesthesia	0	2 (2%)	0	0		2
NSAID (orally/rectally)	28 (17%)	21 (23%)	50 (44%)	8 (35%)		107 (28%)
Conscious sedation	19 (12%)	0	10 (9%)	0		29 (7%)
Unknown	16 (10%)	11 (12%)	24 (21%)	1		52 (13%)
Missing	14	21	20	10		65
Method of ICBT					0.0075	
Tandem + vaginal applicator	146 (82%)	86 (83%)	96 (73%)	24 (77%)		352 (79%)
Tandem only	24 (14%)	4 (4%)	2 (1%)	0		30 (7%)
Vaginal applicator	7 (4%)	11 (10%)	4 (3%)	0		22 (5%)
Unknown	0	3 (3%)	30 (23%)	7 (23%)		40 (9%)
Missing	0	7	2	1		10

*Patients treated with a combination of HDR-ICBT and LDR-ICBT.
HDR, high-dose-rate; ICBT, intracavitary brachytherapy; LDR, low-dose-rate; MDR, medium-dose-rate; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug.

A single dose ≥800 cGy was rarely applied. Single dose HDR-ICBT use was significantly lower in A2 than those of other strata.

The median total dose of EBRT delivered to the central pelvis (point A) and the lateral pelvis (point B) was 3220 and 5000 cGy, respectively. The median total dose of ICBT at point A was 2400 cGy for HDR and 2850 cGy for LDR. Consequently, the median summated point A dose from EBRT and ICBT was 5800 cGy (range 1196–8820) for HDR, and 6974 cGy (range 4464–9160) for LDR.

Table 5 shows the total radiotherapy doses in patients treated with HDR-ICBT according to the FIGO stage. FIGO stage significantly affected the EBRT doses to the central pelvis (point A). In contrast, total point A dose from HDR-ICBT was not affected by stage. The cumulative point A dose of EBRT and HDR-ICBT increased significantly with increasing FIGO stage. The total dose to the lateral pelvis (point B) from EBRT also varied significantly by FIGO stage, although those median values were almost the same. Some patients with stage III/IV received a total point B dose of >6000 cGy.

Table 4. Dosage* of radiotherapy according to the stratification of institutions

Dose (cGy)	Stratification of institutions				*P*-value	Total
	A1	A2	B1	B2		
EBRT						
Total point A dose					0.0021	
0–1999	8 (6%)	8 (10%)	2 (3%)	5 (24%)		23 (8%)
2000–2999	12 (9%)	17 (21%)	11 (16%)	2 (10%)		42 (14%)
3000–3999	56 (41%)	23 (29%)	33 (47%)	7 (33%)		119 (38%)
4000–4999	32 (23%)	18 (23%)	3 (4%)	4 (19%)		57 (18%)
5000+	30 (21%)	14 (17%)	22 (30%)	3 (14%)		69 (22%)
Missing	5	8	4	0		17
Median	3240	3960	3060	3060		3220
Total point B dose					<0.0001	
0–1999	0	0	0	0		0
2000–2999	0	1	1	2 (11%)		4 (1%)
3000–3999	1	4 (5%)	2 (3%)	0		7 (2%)
4000–4999	27 (20%)	22 (28%)	5 (7%)	5 (26%)		59 (19%)
5000–5999	109 (79%)	46 (60%)	61 (87%)	11 (58%)		227 (74%)
6000+	1	5 (6%)	1	1		8 (3%)
Missing	5	10	5	2		22
Median	5000	5000	5000	5000		5000
HDR-ICBT						
Single point A dose					<0.0001	
0–499	6 (4%)	9 (11%)	1 (2%)	0		16 (5%)
500–599	42 (30%)	37 (43%)	11 (18%)	10 (48%)		100 (33%)
600–699	73 (52%)	32 (38%)	29 (48%)	11 (52%)		145 (47%)
700–799	19 (14%)	5 (6%)	19 (32%)	0		43 (14%)
800+	0	2 (2%)	0	0		2 (1%)
Missing	3	3	15	0		21
Median	600	575	600	600		600
Total point A dose					0.02	
0–999	2 (1%)	2 (3%)	0	0		4 (1%)
1000–1999	46 (33%)	18 (23%)	10 (17%)	6 (29%)		80 (26%)
2000–2999	53 (38%)	52 (59%)	29 (48%)	11 (52%)		145 (48%)
3000–3999	39 (28%)	13 (15%)	21 (35%)	4 (19%)		77 (25%)
4000+	0	0	0	0		0
Missing	3	3	15	0		21
Median	2400	2400	2400	2045		2400
EBRT + HDR-ICBT						
Total point A dose					0.0022	
0–3999	6 (4%)	7 (8%)	4 (7%)	4 (19%)		21 (7%)
4000–4999	21 (16%)	11 (14%)	3 (5%)	4 (19%)		39 (13%)
5000–5999	47 (35%)	25 (31%)	20 (34%)	6 (29%)		98 (33%)
6000–6999	33 (24%)	28 (35%)	17 (29%)	4 (19%)		82 (28%)
7000+	29 (21%)	10 (12%)	15 (25%)	3 (14%)		57 (19%)
Missing	7	7	16	0		30
Median	5800	5730	6000	5200		5800

A total of 327 patients were treated with HDR-ICBT with a combination of tandem and vaginal applicator, or tandem only.
*Dose at left side.
HDR-ICBT, high-dose-rate intracavitary brachytherapy; EBRT, external beam radiotherapy.

Table 5. Dosage* of radiotherapy according to the FIGO stage

Dose (cGy)	Missing (*n*)	Stage					*P*-value	Total
		I	II	III	IVA	Other		
EBRT								
Total point A dose							<0.0001	
0–1999	0	7 (35%)	9 (8%)	6 (4%)	1	0		23 (8%)
2000–2999	0	7 (35%)	21 (21%)	14 (9%)	0	0		42 (14%)
3000–3999	1	3 (15%)	29 (28%)	79 (49%)	7 (28%)	0		118 (38%)
4000–4999	0	3 (15%)	22 (22%)	23 (14%)	9 (36%)	0		57 (18%)
5000+	0	0	21 (21%)	40 (24%)	8 (32%)	0		69 (22%)
Missing	2	9	2	3	0	1		17
Median		2180	3060	3240	4060			3220
Total point B dose							<0.0001	
0–1999	0	0	0	0	0	0		0
2000–2999	0	2 (10%)	1	1	0	0		4 (1%)
3000–3999	0	0	2	3 (2%)	2 (8%)	0		7 (2%)
4000–4999	0	10 (50%)	17 (17%)	29 (18%)	3 (12%)	0		59 (20%)
5000–5999	1	8 (40%)	81 (80%)	120 (76%)	17 (68%)	0		226 (74%)
6000+	0	0	0	5 (3%)	3 (12%)	0		8 (3%)
Missing	2	9	3	7	0	1		22
Median		4830	5000	5000	5000			5000
HDR-ICBT								
Total point A dose							0.33	
0–999	0	0	0	3 (2%)	1	0		4 (1%)
1000–1999	0	5 (18%)	25 (25%)	42 (28%)	8 (35%)	0		80 (26%)
2000–2999	1	14 (50%)	47 (48%)	70 (46%)	13 (56%)	0		144 (48%)
3000–3999	2	9 (32%)	27 (27%)	37 (24%)	1	1		75 (25%)
4000+	0	0	0	0	0	0		0
Missing	0	1	5	13	2	0		21
Median		2500	2400	2400	2177			2400
EBRT + HDR-ICBT								
Total point A dose							0.0002	
0–3999	0	12 (48%)	4 (4%)	5 (3%)	0	0		21 (7%)
4000–4999	0	4 (16%)	18 (19%)	14 (9%)	3 (13%)	0		39 (13%)
5000–5999	1	6 (24%)	35 (36%)	53 (35%)	3 (13%)	0		97 (33%)
6000–6999	0	2 (8%)	15 (15%)	53 (35%)	13 (57%)	0		83 (28%)
7000+	0	1	25 (26%)	26 (17%)	4 (17%)	0		56 (19%)
Missing	2	4	7	14	2	1		30
Median		4020	5600	6000	6390			5800

A total of 327 patients were treated with HDR-ICBT with a combination of tandem and vaginal applicator, or tandem only.
*Dose at left side.
HDR-ICBT, high-dose-rate intracavitary brachytherapy; EBRT, external beam radiotherapy.

Overall treatment time (OTT) could be calculated for all 591 patients. The median OTT including ICBT was 49 days. OTT exceeded 8 weeks (56 days) in 193 patients (33%), and 10 weeks (70 days) in 59 patients (10%). There was no significant variance in OTT by either institutional strata or FIGO stage. An unplanned treatment break occurred in 56 out of 565 patients (10%). Patients whose treatment period included consecutive national holidays (e.g. holidays from April 29 to May 5, the year end's and the New year's holidays) had significantly longer OTT ($P = 0.023$). The median OTT was 58 days for

patients with these national holidays during their treatment period (n = 140), and 48 days for those without (n = 451). Sixty-eight out of 193 patients (35%) with OTT >8 weeks were those whose treatment period included the consecutive national holidays.

Chemotherapy

Data on chemotherapy application were collected for 574 patients (97%). One hundred and forty patients (24%) received chemotherapy. Use of chemotherapy significantly varied according to FIGO stage (P = 0.001). Chemotherapy was administered in eight patients (15%) in stage I, 22 patients (13%) in stage II, 87 patients (32%) in stage III and 21 patients (28%) in stage IVA.

Neoadjuvant chemotherapy (NAC) prior to radiotherapy was given in 81 of 574 patients (14%). Twenty-eight of 574 patients (5%) were treated with concurrent chemoradiation. The most frequently used agent for concurrent chemoradiation was bleomycin/pepleomycin, and it was followed by oral 5-fluorouracil. No patients received cisplatin concurrently with radiotherapy.

DISCUSSION

This study demonstrated the national practice patterns for cervical cancer patients treated with radiotherapy without planned surgery between 1995 and 1997 in Japan. Several significant variances in the process according to the stratification of institutions were also observed.

Status of patient background, such as age and KPS, were unfavorable compared with the JPCS data of post-operative radiotherapy for the same period (3). This tendency was also observed when compared with the US PCS (4,5). This might imply that radiotherapy without surgery was mainly given to patients with unfavorable general conditions in Japan. This was also suggested by the distribution ratio of stage I/II patients. Whereas the ratio in the US PCS was ~70% (5,6), it was only 39% in this study. Many investigators demonstrated that definitive radiotherapy brought equivalent outcomes to radical surgery in respectable stage I/II disease (7). Furthermore, a randomized trial clearly confirmed this hypothesis in 1997 (8). The present study identified that patient backgrounds varied by institutional strata. In addition to the factors mentioned above, the hemoglobin value was found to affect the outcome. Several investigators indicated that the pre-treatment hemoglobin value was one of the important prognostic indicators for uterine cervical cancer patients treated with radiotherapy (9). Patients in A1 institutions tended to be favorable for these patient-related factors. This was consistent with the previous JPCS survey (2). This suggested that patients with definitive status tended to be treated at large academic institutions, when radical radiotherapy was attempted. Concerning histology, most patients (95%) had squamous cell carcinoma. The breakdown in histology was different from that of the JPCS data of post-operative radiotherapy (3) and the US PCS (1996–1999) (6). Squamous cell carcinoma was found in 83% of patients in both the JPCS post-operative radiotherapy data and the US PCS (3,6). This might reflect the majority opinion of Japanese gynecological oncologists, i.e. radiotherapy is less effective for cervical adenocarcinoma despite some encouraging treatment results of radical radiotherapy (10,11).

As mentioned above, >60% of the patients were stage III/IV in this survey. The distribution ratio was higher than that of the US PCS (5,6). However, this observation should be interpreted with caution. The incidence of hydronephrosis/non-functioning kidney (23%) in stage III patients demonstrated in this study was lower than that of the US PCS (41%) (5). This suggested that some type of overstaging migration existed in Japan. Eifel has stressed the importance of accurate staging closely adhering to the FIGO notes and rules (12,13). Besides the FIGO stage, we consider that tumor size assessment using MRI could be one of the effective means to evaluate and compare tumor status among different institutions and countries. Although MRI is not permitted to be used in the FIGO staging system, its usefulness in measuring cervical tumor diameter has been demonstrated in several studies (14,15). In evaluation of lymph node status, the present study showed that CT was most commonly used. The same observation was made in the US PCS (5,6). However, lymphangiography and surgical exploration were rarely performed in this survey, although certain numbers of patient were evaluated with these examinations in the USA (5,6). Pre-treatment studies should be investigated further in the next survey using a revised data format.

Several interesting findings were demonstrated regarding methods of EBRT. The most common category of beam energies was 10–14 MV. A beam energy of ≥15 MV was used in <10% of patients. Concerning beam arrangement, the majority of the patients were treated with AP–PA opposite portals. The four-field technique was rarely applied. These treatment parameters are quite different from those demonstrated in the US PCS. In the US PCS survey, a beam energy of ≥15 MV was most frequently used, and 80% of patients were treated with the four-field technique (5). One might claim that the process of EBRT observed in the JPCS is inappropriate to achieve proper dose distribution. However, we consider that the physique of patients, such as antero-posterior (AP) separation, should be taken into account to evaluate the appropriateness of EBRT. While we did not directly collect the data of AP separation, height and weight of the patients were documented in this study. Median height and weight demonstrated in this series should be quite a lot smaller than those of the US patients. We consider that simple beam arrangement using medium beam energy might be sufficient for the majority of Japanese patients. However, this survey also revealed that 20–30% of the patients of A2 and B2 institutions were treated with linear accelerators of <6 MV or Co-60 machines. When only these insufficient beams can be used, we consider that the four-box field technique should be applied, even for small patients. Although RTOG79-20 has

demonstrated the therapeutic value of extended field radiotherapy (16), it had not penetrated into clinical practice during the surveyed period. This was also shown in the 1992–1994 US PCS survey (5). An MLB was used in ~70% of the patients during a part of their treatment course of EBRT. The rate was higher than that of the US PCS (5). A difference in the beam arrangements mentioned above might be one of the reasons. It is difficult to add the MLB for the four-field technique. The present study showed that facility type significantly affected the use of the MLB. We speculate that this closely relates to the application of ICBT.

The US PCS has demonstrated that the use of ICBT significantly improved survival and reduced local failures over EBRT alone (17,18). Nevertheless, the utilization rate of ICBT was lower than expected in the present study. The utilization varied significantly according to the types of institution. We consider that this relates to the problems of institutional infrastructure of radiotherapy in Japan (19). Inoue revealed that brachytherapy equipment and the number of staff were insufficient especially in small non-academic institutions in Japan (19). This survey demonstrated that most patients were treated with HDR-ICBT in all institutional strata. In contrast, the latest US PCS survey (1996–1999) showed that only 12% of the patients were treated with HDR-ICBT (6). We consider that this is one of the most remarkable differences between the USA and Japan. Concerning brachytherapy sources, Co-60 was mostly used, followed by Ir-192. Ir-192 was used more frequently in A1 institutions compared with other strata. In 2002, a quality assurance committee of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) recommended that old HDR machines with Co-60 sources should be replaced with the new type of HDR machines (20). In consequence, the use of Ir-192 sources would be increasing. It is important to note that ICBT applicator insertion was performed without any sedation for about half of the patients. Furthermore, the methods are deemed to be almost insufficient even for sedated patients, such as those receiving orally or rectally administrated NSAIDs. The American Brachytherapy Society (ABS) recommended routine conscious sedation for HDR-ICBT applicator insertions whenever possible (21). The fraction size of HDR-ICBT was within 800 cGy for almost all patients in this survey. This met the recommendation of the ABS and the Gynecologic Oncology Group (GOG) (21,22). The ABS proposed some other technical issues concerning HDR insertion, such as a method of normal tissue displacement, and dose specification (21). These issues should be monitored in detail to assess the quality of ICBT in the next JPCS survey.

We found that there was an obvious difference in total radiation dose of EBRT and HDR-ICBT between the USA and Japan. Although simple dose summation of EBRT and HDR-ICBT is not appropriate, the median total point A dose was 7480 cGy in the US PCS (5) and 5800 cGy in this JPCS series. We consider that this is also one of the remarkable differences in the treatment process between the two countries. This discrepancy was also observed in previously published clinical studies (23–26). We think that it may be closely related to the difference in standard treatment schedules in both countries. A Japanese guideline of radiotherapy has been established for the treatment of uterine cervical cancer by the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Radiological Society (JRS) in 1987. Its English version came out in 1999 (27). Total doses of EBRT and HDR-ICBT used for patients in this survey were almost the same as the recommended schedules in the guideline. We consider that the majority of patients in this survey were treated in accordance with the guideline. In contrast, the ABS recommended doses are higher than those of the Japanese guideline (21). We consider that there are no conclusive clinical data regarding the optimum radiotherapy schedule for uterine cervical cancer. The outcome analysis using PCS data could be one of the measures to solve this problem.

Several investigators indicated that prolonged OTT reduced the pelvic control rate for patients with uterine cervical cancer (28,29). The ABS recommended that the OTT should be kept within 8 weeks (21). The median OTT of this study (49 days) was shorter than that of the US PCS (63 days) (5). However, the OTT exceeded 8 weeks for >30% of the patients in this JPCS series. Further effort should be made to shorten the OTT. The present analysis revealed that consecutive national holidays had a negative influence on the OTT. We consider this to be one of the important problems to be solved.

Approximately one-quarter of the patient received chemotherapy in this survey. Although several randomized clinical trials (RCTs) had failed to demonstrate any positive prognostic value of NAC prior to radiotherapy in the early 1990s (30), this study showed that not a small number of patients were treated with NAC. This indicated that the negative results had not yet penetrated into clinical practice during this period in Japan. On the other hand, concurrent chemoradiotherapy was applied to only 5% of the patients. In 1999, several RCTs demonstrated the survival benefit of concurrent chemoradiotherapy compared with radiotherapy alone (31). We consider that the increasing application of concurrent chemoradiotherapy will be observed in the next JPCS survey.

In conclusion, the JPCS established the national practice patterns of care for uterine cervical cancer patients treated with radiotherapy without planned surgery between 1995 and 1997 within Japan. This survey demonstrated that the institutional strata significantly affected several practice patterns. Some practice patterns were remarkably different from those established by the US PCS. Further improvements in pre-treatment evaluation including staging, and the method of EBRT and ICBT are necessary.

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Postoperative Radiotherapy for Uterine Cervical Cancer: Results of the 1995–1997 Patterns of Care Process Survey in Japan

Takafumi Toita[1], Norio Mitsuhashi[2], Teruki Teshima[4], Katsuya Maebayashi[2], Katsumasa Nakamura[3], Yutaka Takahashi[4], Toshihiko Inoue[5] and a Japanese PCS Working Subgroup for Uterine Cervical Cancer

[1]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, [2]Department of Radiology, Tokyo Women's Medical University, Tokyo, [3]Department of Clinical Radiology, Graduate School of Medical Science, Kyushu University, Fukuoka, [4]Department of Medical Engineering, Osaka University Medical School, Osaka and [5]Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

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Objective: To determine the average national practice of postoperative radiotherapy for uterine cervical cancer in Japan.
Methods: The Japanese Patterns of Care Study (PCS) reviewed the process of care employed for 455 uterine cervical cancer patients who were treated with surgery followed by postoperative radiotherapy (RT) during 1995–1997. Cases with missing data were excluded from calculations of percentage and significance for each of the surveyed items.
Results: According to FIGO stages, 198 patients (45%) were in stage I, 52 patients (12%) were in stage IIA, 146 patients (33%) were in stage IIB and 46 patients (10%) were in stage III/IVA. The most common surgical procedure among the patients was radical hysterectomy (73%). Three hundred and seventy patients (82%) were treated with external beam RT (ERT) alone, and 74 patients (17%) were treated with a combination of ERT and intracavitary RT (ICRT). A midline block was used for the pelvic field in 63 patients (14%). Only seven patients (2%) were treated with extended field ERT. Pelvic ERT was most often performed using AP-PA opposed fields for 431 patients (97%). A majority of the patients (312 patients, 70%) were treated with a total dose of 45.0–50.4 Gy for ERT. Chemotherapy (CT) was administered to 178 patients (40%), neoadjuvant preoperative CT was administered to 80 patients (22%) and concurrent CT with postoperative RT was administered to 29 patients (8%).
Conclusion: This PCS established the national practice average of postoperative RT for uterine cervical cancer. Follow-up studies need to be conducted to determine whether the observed differences in treatment processes affect outcomes.

Key words: cervix neoplasms – radiotherapy – adjuvant

INTRODUCTION

Although several retrospective studies (1) and one randomized clinical trial (2) have demonstrated that both surgery and radiotherapy produce equivalent cure rates, surgery has been widely chosen as a primary treatment for patients with early stage uterine cervical cancer. Postoperative adjuvant radiotherapy (RT) has been administered to selected patients with unfavorable histopathologic findings in their surgical specimens.

The Patterns of Care Study (PCS) has conducted a national survey to measure the structure, process and outcome for patients with uterine cervical cancer, who were treated with radical RT (non-surgery) since 1974 in the US. Several important findings of the process and outcomes have been demonstrated from the US PCS surveys (3–5). However, the US PCS excluded patients who were treated with surgery and postoperative RT. Although numerous data from retrospective studies were available, national practice standards of postoperative RT for uterine cervical cancer have not been systemically reviewed either in the US or in Japan.

A Japanese PCS working group initiated a nationwide survey of four major types of cancers (cervix, esophagus, lung and breast) in 1998. Patients treated with surgery prior to RT were also eligible for the Japanese PCS survey. Therefore, we were able to collect the data regarding surgically treated patients with uterine cervical cancer.

The purpose of this study is to determine the national practice average of postoperative RT for uterine cervical cancer in Japan.

For reprints and all correspondence: Takafumi Toita, Department of Radiology, University of the Ryukyus School of Medicine, 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan.
E-mail: b983255@med.u-ryukyu.ac.jp

METHODS

The Japanese PCS working group carried out an extramural survey of institutions for radiation treatment from September 1998 to March 2001. This group developed an original data format for patients with uterine cervical cancer. Of the total 556 institutions, 73 were selected for the survey by a stratified two-staged cluster sampling method. The data collection method comprised of two steps of random sampling. Prior to the random sampling, all the institutions were classified into four groups. The Japanese PCS classified the Japanese institutions as follows (6): (a) A1—academic institutions, cancer centers/university hospitals treating ≥300 patients/year, (b) A2—academic institutions, cancer centers/university hospitals treating <300 patients/year, (c) B1—non-academic institutions and other national, prefectural, municipal or private hospitals treating ≥120 patients/year and (d) B2—non-academic institutions and other national, prefectural, municipal or private hospitals treating <120 patients/year.

In the first step, the institutes were randomly selected from each group. In the second step, eligible patients were randomly selected from each of the sampled institutions. For the following analyses, the four institutional classifications listed above were combined into two groups, namely, A institutions and B institutions. The eligibility criteria of the Japanese PCS for inclusion in the uterine cervical cancer study were as follows: (a) Patients with carcinoma, (b) patients treated from 1995 to 1997, (c) patients without distant metastases, (d) patients without prior or concurrent malignancies, (e) patients without gross para-aortic lymph node metastases and (f) patients who had not received previous pelvic irradiation.

The Japanese PCS collected clinical data on 1065 patients with uterine cervical cancer, who were treated with RT between 1995 and 1997. Data from 455 of these patients who were treated with surgery and postoperative RT were subjected to the following analyses. The Japanese PCS surveyors comprised 20 radiation oncologists from 10 academic institutions. One radiation oncologist visited and surveyed the data by reviewing the patients' charts for each of the institutions.

The data of past history, pretreatment work-up and treatment were collected. The following parameters were evaluated for the past history: previous minor/major abdominopelvic surgery, pulmonary disease, cardiovascular disease, diabetes, collagen vascular disease, inflammatory bowel disease, HIV status and PID. Pretreatment work-up included the following: Karnofsky performance status, height, weight, hemoglobin value, transfusion, histology, tumor markers (SCC and CEA), clinical FIGO stages, diameter of tumor assessed by MRI (T2WI) and nodal status assessed by CT/MRI. Treatments were surveyed for each modality such as surgery, radiotherapy and chemotherapy. Regarding surgery, the type of surgery, number of resected lymph nodes and pathological data of surgical specimens were evaluated. Pathological findings surveyed were as follows: surgical margin status, tumor size (longest and shortest diameters), lymphovascular space involvement, depth of stromal invasion, pathological T stage, pathological N stage and number of metastatic lymph nodes. Details of the treatment method of RT were evaluated. Parameters for external beam RT (ERT) included the following: method of simulation, utilization of midline block, photon energy, technique (i.e. anteroposterior opposed fields and four-field), treatment volume, total dose, daily dose and unplanned treatment breaks. Parameters for intracavitary brachytherapy were as follows: applicator type, radionuclide, sedation, total dose, daily dose and dose-rate. Application of an approved investigational protocol was also surveyed.

Statistical significance was tested by the chi-square test. Cases with unknown values were included; however, cases with missing values were not included in calculations of percentage and significance.

RESULTS

A institutions included 202 patients (A1: 168, A2: 134) and B institutions included 153 patients (B1: 101, B2: 52).

Table 1 shows the patient characteristics. Of the total 455 patients, 80 patients (18%) were below the age of 40 years and 44 patients (10%) were above the age of 70 years. The median height of the patients was 153 cm, with a range of 130–170 cm (n = 299), and their median weight was 52 kg, with a range of 34–100 kg (n = 313). The Karnofsky performance status (KPS) of A institutions was significantly better than that of B institutions. According to the FIGO classification, 43% of the patients had stage IIB disease or greater (IIB, IIIA/B and IVA).

Table 2 shows the types of surgical procedures employed. The most common surgical procedure was radical hysterectomy, and this was followed by extended radical hysterectomy. Radical hysterectomy was performed more frequently in A institutions than in B institutions. The median number of resected lymph nodes was 19, with a range of 0–90 (n = 207).

Table 3 shows the pathological findings of surgical specimens. Although the availability of data regarding surgical margin status and pelvic nodal status was high, about half of the cases for stromal invasion and lymphovascular space involvement were missing. The pathological tumor diameter was recorded for only 121 patients (27%).

Table 4 shows parameters of RT. A majority of the patients were treated with ERT alone. Intracavitary RT (ICRT) to the vaginal cuff was performed for 80 patients (18%). ICRT was utilized more frequently in A institutions than in B institutions. Utilization rates for ICRT were 38% (29/76) for patients with positive surgical margins and 11% (36/329) for those with negative surgical margins. A midline block was used for the pelvic field in 63 patients (14%). No significant difference was observed in the utilization of midline block between A institutions and B institutions. Utilization rates of midline block were 75% (53/70) for patients treated with ICRT and 3% (10/370) for those with no ICRT. Machine energies used in A institutions were significantly higher than those used in B institutions. Most patients received only whole-pelvis treatment with ERT. Only seven patients (2%) were treated with extended fields that included the para-aortic region. Pelvic ERT was

Table 1. Patient characteristics

Characteristic	No. of patients* (%)	Type of institution		P value
		A	B	
Age (years)				
Range	25–90	25–90	28–85	
Median	52	52	53	
KPS				0.035
≤70	19 (4%)	10 (3%)	9 (6%)	
80	89 (20%)	50 (17%)	39 (26%)	
90–100	336 (76%)	232 (80%)	104 (68%)	
Missing	11	10	1	
Hemoglobin (g/dl)				0.159
<10	112 (26%)	79 (28%)	33 (22%)	
10–12	158 (36%)	100 (35%)	58 (38%)	
>12	101 (23%)	70 (24%)	31 (21%)	
Unknown	65 (15%)	36 (13%)	29 (19%)	
Missing	19	17	2	
Histology				0.067
Squamous	376 (83%)	258 (86%)	118 (79%)	
Adenocarcinoma	43 (10%)	23 (8%)	20 (13%)	
Adenosquamous	28 (6%)	16 (5%)	12 (8%)	
Others	4 (1%)	4 (1%)	0	
Missing	4	1	3	
FIGO stage				<0.0001
I	198 (45%)	116 (39%)	82 (55%)	
II	1	1	0	
IIA	52 (12%)	39 (13%)	13 (9%)	
IIB	146 (33%)	110 (37%)	36 (24%)	
III/IVA	46 (10%)	29 (10%)	17 (12%)	
Missing	12	6	6	

*Total No. = 455.

Table 2. Type of surgical procedure

Surgical procedure	No. of patients	Type of institution	
		A	B
Extended radical hysterectomy	70 (15%)	31 (10%)	39 (25%)
Radical hysterectomy	330 (73%)	240 (79%)	90 (59%)
Modified radical hysterectomy	18 (4%)	11 (4%)	7 (5%)
Total (simple) hysterectomy	27 (6%)	15 (5%)	12 (8%)
Others	9 (2%)	5 (2%)	4 (3%)
Missing	1	0	1

$P < 0.011$.

Table 3. Pathological findings

Pathological findings	No. of patients (%)	Type of institution		P value
		A	B	
Surgical margin				0.4073
Yes	77 (18%)	52 (18%)	25 (18%)	
No	333	225	108	
Unknown/others	15	7	8	
Missing	30	18	12	
Pelvic nodal metastases				0.7279
Yes	159 (38%)	110 (39%)	49 (36%)	
No	245	163	82	
Unknown/others	18	11	7	
Missing	33	18	15	
Deep stromal invasion (> 2/3)				0.7597
Yes	133 (65%)	77 (63%)	56 (67%)	
No	67	42	25	
Unknown/others	6	4	2	
Missing	249	179	70	
Lymphovascular involvement				0.0423
Yes	169 (79%)	124 (83%)	45 (70%)	
No	45	26	19	
Unknown/others	0	0	0	
Missing	231	152	89	

most often administered with anterior and posterior opposed fields. Only 12 patients (2%) were treated with a four-field technique. The median total dose of pelvic ERT was 50 Gy. Three hundred and twelve patients (70%) were treated with a total dose of 45.0–50.4 Gy. The most commonly used daily dose of ERT was 1.8 Gy (52%), this was followed by 2.0 Gy (41%).

The median interval from surgery to the start of RT was 28 days, with a range of 8–230 days ($n = 445$). The median overall treatment time from initiation of RT to completion was 39 days, with a range of 1–120 days. Four hundred and thirty patients (95%) completed the planned treatment.

Chemotherapy was administered to 178 patients (40%). Of these, 118 patients (68%) received chemotherapy including platinum agents. Preoperative neoadjuvant chemotherapy (NAC) was administered to 80 patients (22%), and concurrent chemotherapy with postoperative RT was administered to 29 patients (8%). The utilization rate of NAC was significantly higher in A institutions than in B institutions ($P = 0.004$). Only five patients (1%) were treated with an investigational protocol.

DISCUSSION

The incidence of adenocarcinoma was high in the postoperative RT group as compared to the non-surgery group (7). This might indicate that patients with cervical adenocarcinoma tend to receive surgical treatment, because most gynecologic oncologists consider adenocarcinomas to be radioresistant. Several investigators have shown that the control of pelvic adenocarci-

Table 4. Radiation treatment

Parameter	No. of patients (%)	Type of institution		*P* value
		A	B	
Treatment method				0.002
ERT alone	370 (82%)	231 (78%)	139 (91%)	
ICRT alone	6 (1%)	4 (1%)	2 (1%)	
ERT+ICRT	74 (17%)	62 (21%)	12 (8%)	
Missing	5	5	0	
Midline block				NS
Yes	63 (14%)	45 (15%)	18 (12%)	
No	382 (86%)	249 (85%)	133 (88%)	
Missing	10	8	2	
Beam energy				<0.001
Co-60	13 (3%)	5 (2%)	8 (5%)	
3–5 MV	63 (14%)	19 (6%)	44 (30%)	
6–9 MV	44 (10%)	11 (4%)	33 (22%)	
10–14 MV	297(66%)	231 (78%)	66 (43%)	
15 MV≤	30 (7%)	30 (10%)	0	
Missing	8	6	2	
Technique				NS
AP-PA	431 (97%)	282 (96%)	149 (99%)	
Four-field	12 (2%)	10 (3%)	2 (1%)	
Others	2 (1%)	2 (1%)	0	
Missing	10	8	2	
Total dose				<0.001
<45 Gy	60 (13%)	36 (12%)	24 (16%)	
45 Gy	65 (14%)	35 (12%)	30 (20%)	
>45–<50 Gy	39 (9%)	34 (11%)	5 (3%)	
50 Gy	114 (26%)	87 (29%)	27 (18%)	
>50–<50.4 Gy	3 (1%)	2 (1%)	1 (1%)	
50.4 Gy	91 (20%)	43 (15%)	48 (32%)	
>50.4 Gy	74 (17%)	58 (20%)	16 (10%)	
Missing	9	7	2	
Daily dose				<0.001
<1.8 Gy	25 (6%)	23 (8%)	2 (1%)	
1.8 Gy	230 (51%)	134 (45%)	96 (64%)	
>1.8–<2.0 Gy	1	0	1 (1%)	
2.0 Gy	184 (42%)	133 (45%)	51 (34%)	
2.0 Gy<	6 (1%)	6 (2%)	0	
Unknown	1	1	0	
Missing	8	5	3	

ERT, external beam radiotherapy. ICRT, intracavitary radiotherapy.

nomas is comparable with that of squamous cell carcinomas, when treatment consisted of radical radiotherapy (8,9). However, the present data suggests that this was not accepted in clinical practice in Japan. Regarding the clinical stages, locally advanced cases (FIGO stage ≥ IIB) were frequently included in this series. This might indicate that a significant number of patients with inoperable stage cancer underwent surgery, probably after NAC in Japan.

Various pathologic risk factors with regard to surgically treated early stage uterine cervical cancer have been identified (10). The availability of data describing these pathologic findings was unsatisfactory, except for the surgical margin status and pelvic nodal status in this survey. This suggested that indications for postoperative RT were determined primarily by the surgical margin and pathological nodal status in Japan. However, we could not directly analyze the indications for postoperative RT in each patient because of the inadequacy of the data format. In the next survey, these data will be available in a revised format.

Several interesting findings were observed with respect to radiation parameters. Although no studies have shown significant therapeutic value of ICRT to the vaginal cuff, 15% of the patients were treated with ICRT. Patients with a positive surgical margin in the vaginal cuff might be considered as candidates for an ICRT boost. However, according to Kim et al. some uncertainties are associated with the dose distribution of the ICRT boost (11). On the other hand, 9% of the patients with negative surgical margins also underwent an ICRT boost. Similarly, indications for a midline block were also unclear. A midline block was utilized not only for patients treated with ICRT but also for those who did not receive ICRT. Both, the efficacy and indications for ICRT boost and midline block should be further explored. Although a published randomized study of the Radiation Therapy Oncology Group (RTOG) showed positive results for prophylactic extended-field RT to the para-aortic region in 1995 (12), this finding was not incorporated in the clinical practice in the intervening time period. Regarding the technique of ERT, almost all patients were treated with the AP-PA opposed fields in this series. In the US PCS, data showed that 70% of the patients were treated with the four-field technique (5). Higher energy was used in the USA than in Japan. The most frequently used X-ray beam energies were ≥15 MV in the USA (5) and 10–14 MV in Japan. From these data, one might consider the technique of ERT practiced in Japan to be inappropriate to obtain an accurate dose distribution in both clinical target volume (CTV) and the surrounding normal organs. However, this finding should be interpreted carefully. An estimation of body size, i.e., AP separation, would be necessary to evaluate the most appropriate method and energy of ERT. The AP separation of Japanese women might be less than that of women in the USA. We consider that the four-field technique should be applied only if a machine with low-beam energy is available.

Although the efficacy of preoperative NAC was not fully determined by phase III trials within this study period, about one fifth of the patients were treated with NAC in this series. NAC was administered not only for operable stage IB patients but also for patients with more advanced, inoperable stages. Almost all of these patients were treated outside an investigational protocol. Patients in academic institutions were more

frequently treated with NAC than those in non-academic institutions. This might indicate that Japanese academic institutions tend to apply new treatment strategies regardless of proven therapeutic evidence. One randomized trial from Argentina demonstrated the positive value of NAC prior to surgery for stage IB uterine cervical cancer in 1997 (14). We suspect that utilization of NAC will become more frequent in the next time period that will be studied. Concurrent chemotherapy with postoperative RT was not widely accepted during the periods in this study. In 2000, a randomized intergroup trial demonstrated a positive impact on prognosis in the case of cisplatin-based chemotherapy administered concurrently with postoperative RT to high-risk early-stage uterine cervical cancer patients (15). Therefore, we suspect that this approach will also be incorporated in the daily clinical practices for uterine cervical cancer patients.

To summarize, this study demonstrates the Japanese national practice average of postoperative RT for uterine cervical cancer during 1995–1997. Follow-up studies will be essential to determine the manner in which the observed differences in process affect treatment outcomes.

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Radical External Beam Radiotherapy for Prostate Cancer in Japan: Preliminary Results of the Changing Trends in the Patterns of Care Process Survey between 1996–1998 and 1999–2001

Kazuhiko Ogawa[1,2], Katsumasa Nakamura[3], Tomonari Sasaki[3], Tokihiro Yamamoto[4], Masahiko Koizumi[5], Toshihiko Inoue[6], Teruki Teshima[4] and the Japanese Patterns of Care Study Working Subgroup on Prostate Cancer

[1]Department of Radiology, University of the Ryukyus, Okinawa, [2]Department of Molecular and Surgical Oncology, Medical Institute of Bioregulation, Kyushu University, Beppu, Kyushu, [3]Department of Clinical Radiology, Kyushu University, Fukuoka, [4]Department of Medical Physics and Engineering, Osaka University, Osaka, [5]Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka and [6]Department of Radiation Oncology, Osaka University, Osaka, Japan

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Objective: To report the preliminary results of a study to delineate the changing trends in radical external beam radiotherapy usage for prostate cancer between the 1996–1998 and 1999–2001 survey periods in Japan.
Methods: The 1996–1998 Patterns of Care Study (PCS) and the 1999–2001 PCS in Japan reviewed the detailed information on 694 patients with prostate cancer treated with radiotherapy. Of them, 298 patients with clinically localized prostate cancer treated with radical external beam radiotherapy in A1 and B1 institutions were selected for analysis (1996–1998 PCS, 117 patients; 1999–2001 PCS, 181 patients).
Results: High-risk prostate cancer (defined as T3–T4 tumors, a pretreatment prostate-specific antigen level >20 ng/ml, and/or poorly differentiated adenocarcinoma) was diagnosed in 82.1% of the patients in the 1996–1998 PCS and in significantly less (70.2%) of those in the 1999–2001 PCS ($P = 0.021$). Moreover, significantly earlier T stages (T1–T2: 49.7%) and more well-differentiated tumors (24.7%) were found between 1999 and 2001 than between 1996 and 1998 (T1–T2: 31.9%, well-differentiated tumors: 13.9%). Although only 6.1% of patients were treated with radiotherapy by patient's choice in 1996–1998, a larger proportion (32.2%) chose this treatment in 1999–2001. The median radiation dose was 65.0 Gy (range, 24–74 Gy) in 1996–1998 and increased to 69 Gy (range, 14–80 Gy) in 1999–2001. The percentage of radiation doses <60 Gy was 20.5% in 1996–1998 but only 2.2% in 1999–2001. Moreover, the incidence of treatment with total doses of ≥70 Gy was higher in 1999–2001 (43.9%) than in 1996–1998 (19.7%). These increased radiation doses were predominantly observed in B1 institutions. Although the usage of ≥10 MV was significantly increased in 1999–2001 (82.0%) compared with that in 1996–1998 (65.8%), conformal therapy administered to 52.1% of patients in 1996–1998 was almost the same (55.8%) in 1999–2001. The median number of full-time equivalent (FTE) radiation oncologists (2.4 in A1 institutions and only 0.6 in B1 institutions) in 1996–1998 increased slightly in 1999–2001 (2.7 in A1 institutions, 0.7 in B1 institutions), but remained low in B1 institutions.
Conclusions: In Japan, there is a trend to fewer high-risk prostate cancer patients being treated with radical external beam radiotherapy. An increasing percentage of patients chose radiotherapy and also increased radiation doses, which might reflect the growing acceptance of radical external beam radiotherapy as a treatment of choice for prostate cancer in Japan. Therefore, to optimize delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted.

Key words: 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

For reprints and all correspondence: Kazuhiko Ogawa, Department of Molecular and Surgical Oncology, Medical Institute of Bioregulation, Kyushu University, Tsurumihara 4546, Beppu 874-0838, Japan.
E-mail: kogawa@med.u-ryukyu.ac.jp

period (1–3). In addition to documenting the practice process, the PCS is important in developing and disseminating national guidelines for cancer treatment. This helps to promote a more uniform care process in the country. The PCS is also designed to complement clinical trials which enhance the standard of care for cancer patients (1,4).

To improve the quality of radiation oncology, the PCS has been imported to Japan from the USA (5,6). The Japanese PCS Working Group on Prostate Cancer started a nationwide process survey for patients who underwent radiotherapy between 1996 and 1998. Subsequently, a second PCS (1999–2001) of patients treated between 1999 and 2001 was conducted and we reported the preliminary results of that PCS for radical external beam radiotherapy in prostate cancer patients in Japan (7–9).

Over the past 10 years, there have been the remarkable changes in prostate cancer treatment policy in Japan. Since entering the prostate-specific antigen (PSA) era, it is possible to detect earlier stages of prostate cancer and there is a better chance of successfully treating early-stage patients with prostate cancer than ever before. Moreover, the use of radical external beam radiotherapy for prostate cancer has been rapidly increasing recently, because a significant amount of new radiation treatment planning technology and methodology has become available. Therefore, to treat Japanese prostate cancer patients optimally, it is important to detect properly the intrinsic changes in the national practice process of radiotherapy for prostate cancer in Japan. In this paper, we report the preliminary results of our study to delineate the changing trends in the process of care for prostate cancer patients treated with radical external beam radiotherapy between the 1996–1998 and 1999–2001 survey periods in Japan.

MATERIALS AND METHODS

The 1996–1998 and the 1999–2001 PCS in Japan reviewed the detailed information on 694 patients with prostate cancer treated with radiotherapy during the respective survey periods (1996–1998 PCS, 307 patients; 1999–2001 PCS, 387 patients). The PCS carried out an extramural audit survey, using a stratified two-stage cluster sampling design. The Japanese PCS developed an original data format in collaboration with the American College of Radiology (ACR, Philadelphia, PA). The PCS surveyors consisted of 20 radiation oncologists from academic institutions. For each institution, one radiation oncologist visited and surveyed data by reviewing patients' charts.

Table 1. Criteria of the institutional stratification in the 1996–1998 and 1999–2001 PCSs

Stratification		No. of patients	
		1996–1998	1999–2001
A1	University Hospital/Cancer Center	≥300/year	≥430/year
A2	University Hospital/Cancer Center	<300/year	<430/year
B1	Others	≥120/year	≥130/year
B2	Others	<120/year	<130/year

To validate the quality of collected data, the PCS utilized an Internet mailing list including all the surveyors. In-site real-time checks and adjustments of the data input were available to each surveyor and the PCS committee (10).

The following eligibility criteria were used in the current survey: the patients were required to have adenocarcinoma of the prostate without evidence of distant metastasis; they had to have been treated with radiotherapy during the 1996–1998 (1996–1998 PCS) and 1999–2001 (1999–2001 PCS) survey periods; and they should not have received diagnosis of any other malignancy or been previously treated with radiotherapy. Patients who had received prior prostatectomy and patients with hormone-refractory prostate cancer were excluded from this analysis.

The criteria for both the 1996–1998 and 1999–2001 institutional stratifications, on the basis of the Japanese facility master list (11,12), are detailed in Table 1. In the current study, the 1999–2001 PCS was a preliminary study of data gathered only from investigating A1 and B1 institutions and by a two-stage cluster sampling scheme (8). Therefore, in the current study, 298 patients with clinically localized prostate cancer treated with radical external beam radiotherapy in A1 and B1 institutions were selected for analysis (1996–1998 PCS, 117 patients from 22 institutions; 1999–2001 PCS, 181 patients from 36 institutions).

For this analysis, patients with either T3 or T4 tumors, a pretreatment PSA level >20 ng/ml and/or poorly differentiated tumors were defined as high-risk disease patients. Statistical analyses were performed using the Statistical Analysis System at the PCS data center (13). Statistical significance was tested using the chi-squared test, Student's *t*-test and the Mann–Whitney *U*-test. A probability level of 0.05 was chosen for statistical significance.

Table 2. Incidences of high-risk* prostate cancer patients in the 1996–1998 and 1999–2001 PCSs

PCS	Total No. of patients	No. of patients		Significance (*P*)
		High-risk	Not high-risk	
1996–1998	117	96 (82%)	21 (18%)	
1999–2001	181	127 (70%)	54 (30%)	0.021

*Defined as T3–T4 tumors, a pretreatment prostate-specific antigen level >20 ng/ml and/or poorly differentiated adenocarcinoma.

Table 3. Patients' and disease characteristics

	PCS		Significance (*P*)
	1996–1998 (*n* = 117)	1999–2001 (*n* = 181)	
Institutions	22	34	
Age (median) (years)	70.1 (46.5–88.2)	72.5 (49.7–98.6)	
Mean ± SD (years)	68.6 ± 13.3	73.1 ± 6.8	0.0018
Missing	2	0	
KPS (median, %)	90 (40–100)	90 (70–100)	
Mean ± SD	87.1 ± 9.2	89.7 ± 6.8	0.0071
Missing	7	5	
Pretreatment PSA level (%)			
Median	22.0 (0.5–900)	20.2 (1.9–515.7)	NS (0.4617)
Mean ± SD	52.5 ± 97.3	45.3 ± 68.3	
<10	33/114 (29.0%)	51/173 (29.5%)	
10–19.9	59/114 (16.7%)	33/173 (19.1%)	NS (0.8438)
≥20	62/114 (54.4%)	89/173 (51.5%)	
Missing	3	8	
Differentiation			
Well	16/115 (13.9%)	43/174 (24.7%)	
Moderate	59/115 (51.3%)	63/174 (36.2%)	0.0409
Poor	34/115 (29.6%)	60/174 (34.5%)	
Missing	2	8	
Gleason combined score (%)			
2–6	8/35 (22.9%)	48/117 (41.0%)	
7	15/35 (42.9%)	26/117 (22.2%)	0.0349
8–10	12/35 (34.3%)	43/117 (36.8%)	
Missing	82	64	
T-stage (%)			
T1	7/116 (6.0%)	12/173 (6.9%)	
T2	30/116 (25.9%)	74/173 (42.8%)	<0.0001
T3	61/116 (52.9%)	70/173 (40.5%)	
T4	17/116 (14.7%)	5/173 (2.9%)	
Unknown	1/116 (0.9%)	5/173 (2.9%)	
Missing	1	8	
N-stage (%)			
N0	94/117 (80.3%)	160/171 (93.6%)	
N1	15/117 (12.8%)	7/171 (4.1%)	0.0026
Unknown	2/117 (1.7%)	3/171 (1.8%)	
Missing	0	10	
Reason for selection of RT (%)			
Patient choice	6/99 (6.1%)	56/174 (32.2%)	
Advanced or high-risk disease	35/99 (35.4%)	49/174 (28.2%)	
Medical contraindication	0/99 (0.0%)	23/174 (13.2%)	<0.0001
Old age	22/99 (22.2%)	28/174 (16.1%)	
Others	13/99 (13.1%)	7/174 (4.0%)	
N/A or unknown	23/99 (23.2%)	11/174 (6.3%)	
Missing	18	7	

KPS = Karnofsky performance status; PSA = prostate-specific antigen; RT = radiotherapy.

Table 4. Treatment characteristics

	PCS		Significance (*P*)
	1996–1998 (*n* = 117)	1999–2001 (*n* = 181)	
Radiotherapy			
Energy (≥10 MV) (%)			
Yes	77/117 (65.8%)	146/178 (86.1%)	0.0015
Missing	0	3	
Were portal films or electric portal images used (%)			
Yes	–	137/178 (77.0%)	–
Missing	–	3	
All field treated each day (%)			
Yes	–	125/181 (69.1%)	
Use of CT simulator (%)			
Yes	98/117 (83.8%)	155/180 (86.1%)	NS (0.5774)
Missing	0	1	
Conformal therapy (%)			
Yes	61/117 (52.1%)	101/181 (55.8%)	NS (0.5351)
Pelvic irradiation (%)			
Yes	30/117 (25.6%)	73/181 (40.3%)	0.0092
Radiation dose (cGy)			
A1 + B1 (total)			
Median (range)	6500 (2400–7400)	6900 (1400–8000)	<0.0001
Mean ± SD	6213.8 ± 900.6	6709.8.6 ± 689.6	<0.0001
Missing	1	0	
A1			
Median (min.–max.)	6600 (2400–7400)	6900 (1400–7600)	0.0029
Mean ± SD	6463.0 ± 749.9	6686.5 ± 775.0	0.0473
B1			
Median (min.–max.)	5050 (3400–7000)	6900 (3000–8000)	<0.0001
Mean ± SD	5491.3 ± 922.2	6738.9 ± 568.6	<0.0001
Hormonal therapy (%)			
Yes	97/116 (83.6%)	160/180 (88.9%)	NS (0.1908)
Missing	1	1	
Chemotherapy (%)			
Yes	17/114 (14.9%)	12/172 (7.0%)	0.0295
Missing	3	9	

RESULTS

Patients' and Disease Characteristics

High-risk prostate cancer (defined as T3–T4 tumors, a pretreatment PSA level >20 ng/ml, and/or poorly differentiated adenocarcinoma) was diagnosed in 82.1% (96 of 117 patients) in the 1996–1998 PCS and in significantly fewer (70.2%, 127 of 181 patients) in the 1999–2001 PCS (Table 2, $P = 0.021$).

Patient and disease characteristics in the 1996–1998 and 1999–2001 PCSs are shown in Table 3. Significantly earlier T stages (T1–T2, 49.7%, $P < 0.0001$) and more well-differentiated tumors (24.7%, $P = 0.0349$) were found between 1999 and 2001 than between 1996 and 1998 (T1–T2, 31.9%, well-differentiated tumor, 13.9%). Table 3 also indicates the reasons for selection of radiotherapy during these different periods. In 1996–1998, only 6.1% (6 of 99) of the patients were treated with radiotherapy by patient's choice. On the other hand, patient's choice became one of the main reasons for this treatment between 1999 and 2001 (32.2%, 56 of 174 patients), which are significantly different (statistical analysis only in terms of 'patient choice': $P < 0.0001$).

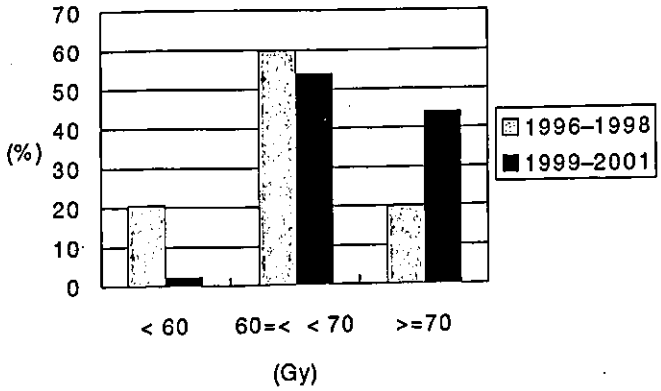

Figure 1. Distribution of external irradiation doses for prostate cancer in the 1996–1998 and 1999–2001 survey periods.

Treatment Characteristics

Treatment characteristics are shown in Table 4. The use of ≥10 MV was significantly increased ($P = 0.0015$) in the 1999–2001 PCS (82.0%) compared with that in the 1996–1998 PCS (65.8%). On the other hand, the rates of CT simulator ($P = 0.5774$) and conformal therapy administration ($P = 0.5351$) were not significantly different and conformal therapy administered to 52.1% of patients in 1996–1998 was almost same (55.8%) in 1999–2001. The median radiation doses in 1996–1998 and 1999–2001 were 65 and 69 Gy, respectively. The percentage of radiation dose <60 Gy was 20.5% in the 1996–1998 PCS but only 2.2% in the 1999–2001 PCS (Fig. 1). Moreover, the incidence of treatment with total doses of ≥70 Gy was higher in 1999–2001 (43.9%) than in 1996–1998 (19.7%). These increased radiation doses were predominantly observed in B1 institutions (Table 4).

In both the 1996–1998 and 1999–2001 survey periods, hormonal therapy was commonly used before, during and after radiotherapy with a mean duration of 1.01 ± 1.04 and 1.31 ± 1.03 years, respectively (83.6% of patients in 1996–1998, 88.9% of patients in 1999–2001, $P = 0.1908$). In contrast, chemotherapy in general was not administered in both periods and significantly less in 1999–2001 (1996–1998, 14.9%; 1999–2001, 6.6%, $P = 0.0295$).

Full-time Equivalent (FTE) Radiation Oncologists

In the 1996–1998 PCS, the median number of FTE radiation oncologists was 2.4 in A1 institutions and only 0.6 in B1 institutions. In the 1999–2001 PCS, the median number of FTE radiation oncologists slightly increased (2.7 in A1 institutions, 0.7 in B1 institutions).

DISCUSSION

This study indicates that Japanese prostate cancer patients treated with radical external beam radiotherapy had significantly less high-risk diseases in 1999–2001 than 1996–1998. Moreover, significantly early primary stage and more well-differentiated tumors were found in 1999–2001 than in 1996–1998. These results suggest that the chances of treating earlier stage prostate cancer patients with radiotherapy are greater than ever before in Japan. Because of the prevailing use of PSA and the increasing number of patients treated with radiotherapy in Japanese institutions (14), the opportunities for treating early-stage prostate cancer patients with radical external beam radiotherapy will increase even more in the future. Recently, interstitial radiotherapy has also been used increasingly in the management of men, with early-stage prostate cancer both in the USA and Japan (15,16). However, at the time of this analysis, only 5.4% (1996–1998 PCS: 307 patients) and 1.1% (1999–2001 PCS: 387 patients) of all patients were treated with interstitial radiotherapy. Therefore, after we have accumulated the data from greater numbers of patients, we will report updated results of interstitial radiotherapy.

This study also revealed that there was a remarkable change in the reason for choosing radiotherapy in Japan between the 1996–1998 and 1999–2001 survey periods. Although only 4.9% of the patients were treated with radiotherapy by their own choice in 1996–1998, 34.6% of patients chose radiotherapy in 1999–2001. External beam radiotherapy did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an inadequate number of radiation oncology centers prevented earlier dissemination of this type of therapy. However, significant amounts of new radiation treatment planning technology and methodology are now available and Japanese patients have recently become aware of the effectiveness of radiotherapy for prostate cancer (17). Therefore, the increasing percentage of those choosing radiotherapy might reflect acceptance of radical external beam radiotherapy as a treatment of choice for prostate cancer patients in Japan.

Moreover, radiotherapy strategy appears to have changed between the 1996–1998 and 1999–2001 survey periods. The radiation doses were higher in the 1999–2001 PCS (median, 69 Gy) than in the 1996–1998 PCS (65 Gy). The percentage receiving radiation doses <60 Gy was 20.5% in 1996–1998, but only 2.2% in 1999–2001 (Fig. 1). Furthermore, the percentage of patients treated with total doses of ≥70 Gy was higher in 1999–2001 (43.9%) than in 1996–1998 (19.7%). These results indicate that lower radiation doses were more common between 1996 and 1998, while higher doses prevailed between 1999 and 2001. The use of increasing radiation dose might reflect the widespread dissemination of clinical trial results (18,19) and also growing acceptance by radiation oncologists and urologists of radical external beam radiotherapy as a main treatment for prostate cancer (20).

However, the national practice process of radiotherapy in Japan was closely related to structural immaturity, especially in terms of equipment and personnel. The rates of CT simulator and conformal therapy administration, technology that not only improves the target volume dose distribution but also concomitantly reduces the normal tissue dose (21), were not significantly different between the 1996–1998 and 1999–2001 survey periods. Especially the rates of conformal therapy remained low (~50%) during these periods. With regard to

personnel, the median number of FTE radiation oncologists slightly increased in 1999–2001, but remained low in B1 institutions. On the other hand, the number of prostate cancer patients treated with radiotherapy has increased in every institution over the past few years (14). Therefore, the amount of advanced equipment and the number of radiation oncologists on duty must be increased in Japanese institutions.

By comparing of the results of the 1996–1998 and 1999–2001 PCSs, we can delineate the changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. There was a trend toward less high-risk diseases between 1999–2001 and 1996–1998 and radical external beam radiotherapy has recently become a treatment of choice for prostate cancer in Japan. Therefore, to optimize the delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted.

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