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CLINICAL INVESTIGATION **Cervix**

PATTERNS OF RADIOTHERAPY PRACTICE FOR PATIENTS WITH CERVICAL CANCER (1999–2001): PATTERNS OF CARE STUDY IN JAPAN

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Purpose: To describe the patterns of definitive radiotherapy practice for patients with uterine cervical cancer from 1999 to 2001 in Japan.

Methods and Materials: The Japanese Patterns of Care Study (JPCS) working group conducted a third extramural audit survey of 68 institutions and collected specific information on 324 cervical cancer patients treated with definitive radiotherapy.

Results: Almost all patients (96%) were treated with whole pelvic radiotherapy using opposing anteroposterior fields (87%). A midline block was used in 70% of the patients. Intracavitary brachytherapy (ICBT) was applied in 82% of cases. Most patients (89%) were treated with high-dose rate (HDR) ICBT. Calculation of doses to organs at risk (ICRU 38) was performed for rectum in 25% of cases and for bladder in 18% of cases. Only 3% of patients were given intravenous conscious sedation during ICBT applicator insertions. The median total biologically effective dose at point A (EBRT+ICBT) was 74 Gy_{10} in cases treated with HDR-ICBT. There was no significant difference in total biologically effective dose between stages. The median overall treatment time was 47 days. Concurrent chemoradiation was applied in 17% of patients.

Conclusions: This study describes the general patterns of radiotherapy practice for uterine cervical cancer in Japan. Although methods of external radiotherapy seemed to be appropriate, there was room for improvement in ICBT practice, such as pretreatment. A substantial difference in total radiotherapy dose between Japan and the United States was observed. © 2008 Elsevier Inc.

Patterns of care study, Cervix, Radiotherapy.

INTRODUCTION

Several randomized controlled trials (RCTs) conducted in the 1990s have demonstrated that concurrent chemoradiotherapy (CCRT) reduced the mortality risk in uterine cervical cancer patients by 30%–50% compared with radiotherapy alone (1–3). Another RCT demonstrated no difference in the survival rates between definitive radiotherapy and surgery for early-stage cancer patients with Stages IB and IIA (4). Consequently, radiation therapy has become the more appropriate option in the treatment of cervical cancer. In the United States, the American Brachytherapy Society (ABS) issued the radiotherapy guidelines for uterine cervical cancer (5, 6), and in Japan, the General Rules for Clinical and Pathological Study of Uterine Cervical Cancer provide treatment guidelines, including the standard treatment schedule of radiotherapy (7). Currently, organizations such as the Gynecologic Cancer Intergroup (GCIG) are trying to set up international clinical trials of radiotherapy for uterine cervical cancer (8). Although international standardization of radiotherapy is an important issue, some between-country differences in the clinical practice of radiotherapy can be expected.

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The Patterns of Care Study (PCS) initially surveyed radiotherapy practice in the United States. The subjects of the survey were selected by the two-staged cluster sampling method (medical institutions and patients) from institutions providing radiotherapy throughout the United States. The national averages for radiotherapy practice can be demonstrated using this method (9). In the United States, PCSs have been conducted for more than 30 years, and the structure, process, and outcome of radiotherapy, as well as various problems in clinical practice, have been identified for uterine cervical cancer (10–13). In Japan, the Japanese Patterns of Care Study (JPCS) began in 1996 and used the same methods (14). We previously reported the PCS results for radiotherapy practice in uterine cervical cancer patients treated in 1992–1994 and 1995–1997 (15, 16). We report here the corresponding results for 1999–2001. We compared the data from this study with those of the preceding JPCS (1995–1997) and the U.S. PCS. The changes over the years in radiotherapy practice were examined for cervical cancer in Japan, and the differences between Japan and the United States were also examined.

METHODS AND MATERIALS

Between July 2002 and June 2004, the JPCS conducted a third national survey of patients with uterine cervical cancer treated with radiotherapy. Eligibility criteria for the survey were as follows: (*1*) carcinoma, (*2*) treated between January 1999 and December 2001, (*3*) no distant metastases, (*4*) no prior or concurrent malignancy, (*5*) no gross para-aortic lymph node metastases, and (*6*) no previous pelvic radiotherapy. Sixty-eight of 640 institutions were selected for the survey using a stratified two-staged cluster sampling method. Before the random sampling, all institutions were classified into four groups. Institutions were classified by type and number of patient treated with radiotherapy. The criteria for stratification have been detailed elsewhere (14). In brief, the JPCS stratified Japanese institutions as follows: A1, academic institutions treating ≥430 patients annually; A2, <430 patients; B1, nonacademic institutions treating ≥130 patients annually; B2, <130 patients. Academic institutions included cancer center hospitals and university hospitals. Nonacademic institutions consisted of other facilities, such as national, prefectural, municipal, and private hospitals.

The JPCS surveyors performed on-site chart review at each participating facility using an originally developed database format for uterine cervical cancer. Data collection included patient characteristics (e.g., patient's history, age, performance status, laboratory data, pathology, and stage), details of pretreatment workup, therapeutic information (e.g., radiotherapy, chemotherapy, and surgery), and treatment outcome. The JPCS collected clinical data on 631 patients with uterine cervical cancer who were treated with radiotherapy from 68 institutions. In this study, 324 patients treated by radiotherapy without planned surgery were analyzed. These included 115 patients from A1 institutions, 70 patients from A2 institutions, 104 patients from B1 institutions, and 35 patients from B2 institutions.

Statistical significance was tested using the chi-square test. Unknown and missing data were combined in the tables because these were the same in most cases: no valid data were found in the given resources (17). Ratios were calculated using unknown or missing data, but continuous variables did not include these data (17), as seen in a U.S. PCS report (18).

RESULTS

Table 1 shows the characteristics of the 324 patients in our survey. In total, 276 patients (85%) were hospitalized for treatment. Of these, 190 patients (59%) were hospitalized during both external beam radiotherapy (EBRT) and brachytherapy, 78 (24%) were hospitalized only during EBRT, and 8 (2%) only during brachytherapy.

External beam radiotherapy

External beam radiotherapy (EBRT) was performed in 320 patients (99%). Twenty-two patients (7%) received EBRT at another facility. In 142 cases (44%), multileaf collimators (MLC) were used to shape the portals. For 308 patients (96%), the planning target volume (PTV) included the whole pelvic region. The upper border of the pelvic field was at the L4 to L5 interspace in 238 of the 308 patients (77%). Only 10 patients (3%) received extended field radiotherapy including the para-aortic region. Treatment parameters of pelvic EBRT are shown in Table 2. The most frequently used beam energy was 10-14 MV X-rays. Pelvic EBRT was most often given using an opposing anteroposterior (AP-PA) technique. The median isocenter depth of the AP-PA portals was 9 cm (range, 6.5–12.9 cm). A midline block was used in 70% of the patients. A single-daily fraction dose of 1.8 or 2.0 Gy was used for most patients.

Brachytherapy

No patient surveyed received interstitial brachytherapy. Table 3 shows the details of intracavitary brachytherapy (ICBT). ICBT was applied in more than 80% of cases. The ICBT application rate by Fédération Internationale de

Table 1. Patient and tumor characteristics of 324 patients with uterine cervical cancer treated with radiotherapy.

Characteristics	No. of patients	(%)
Total no.	324	
Age (yrs)		
Range	26-100	
Median	71	
KPS		
<=70	64	20
80	103	32
90	114	35
100	21	6
Unknown/missing	22	7
Histology		
Squamous cell carcinoma	300	93
Adenocarcinoma	14	4
Adenosquamous cell carcinoma	4	1
Other	2	1
Unknown/missing	4	1
FIGO stage		
I	43	13
II	102	31
III	122	38
IVA	35	11
Unknown/missing	22	7

Table 2. Treatment parameters of pelvic external beam radiotherapy

Parameters	*n*	%
Beam energy		
Co-60	2	1
3–5 MV	30	10
6–9 MV	45	15
10–14 MV	220	71
15 MV	9	3
other	0	0
Unknown/missing	2	—
Technique		
AP-PA	269	87
Four-field box	21	7
Other	17	6
Unknown/missing	1	—
Midline block		
Yes	215	70
No	72	23
Unknown/missing	21	7
Daily fraction size (Gy)		
<1.8	25	8
1.8	135	44
1.8–2	2	1
2	137	45
>2	6	2
Missing	3	—

Gynécologie Obstétrique (FIGO) stages was 88% for Stage I, 88% for Stage II, 89% for Stage III, and 51% for Stage IVA. Its application was significantly less frequent in stage IVA patients (p <0.0001). Sixty-four patients (25%) received ICBT at another facility. Approximately 90% of the patients were treated with high-dose rate (HDR) ICBT. The most frequent radionuclide for ICBT source was cobalt-60 (Co-60), followed by iridium-192 (Ir-192). A rigid-type applicator was used for about 60% of the patients. In vivo rectal dosimetry was performed in approximately one quarter of the patients, whereas bladder dosimetry was rarely performed. ICRU 38 reference doses at the rectum and bladder were calculated in one quarter or less of the patients. Supportive medication before or during the applicator insertion was almost never given; when it was administered, it seemed to be inadequate. The dose calculation was performed for every HDR-ICBT fraction for more than three quarters of the patients. In most patients, all HDR-ICBT procedures (applicator insertion, radiograph generation and treatment) were performed in the same room.

Radiation dose and overall treatment time

Table 4 shows radiotherapy dose as a function of the FIGO stage. Total EBRT dose to the central pelvis (point A dose) significantly increased with increasing FIGO stage. Although a significant difference was also observed in total dose to the lateral pelvis (point B dose), median dose was almost the same at all stages. Median ICBT fraction size at point A was 524 cGy for HDR and 1740 cGy for LDR. The most frequent HDR-ICBT dose per fraction at point A was 500–599 Gy (79/215, 37%), followed by 600–699 cGy (48/215, 22%),

Table 3. Details of intracavitary brachytherapy

Parameters	*n*	%
ICBT given		
Yes	265	82
No	58	18
Unknown/missing	1	0
Dose rate		
HDR	215	89
LDR	27	11
HDR+LDR	0	0
Other	0	0
Unknown/missing	23	-
Source		
Co-60	112	46
Ir-192	102	42
Cs-137	21	9
Ra-226	7	3
Unknown/missing	23	-
Method of ICBT		
Tandem + vaginal applicator	202	83
Tandem only	26	11
Vaginal applicator	16	6
Unknown/missing	21	-
Applicator		
Rigid	166	63
Nonrigid	66	25
Unknown/missing	33	12
In vivo dosimetry: bladder		
Yes	8	3
No	207	78
Unknown/missing	50	19
In vivo dosimetry: rectum		
Yes	71	27
No	145	55
Unknown/missing	49	18
ICRU38: bladder		
Yes	48	18
No	146	55
Unknown/missing	71	27
ICRU38: rectum		
Yes	65	25
No	128	48
Unknown/missing	72	27
Preparation		
None	90	54
NSAIDs; orally/rectally	68	41
IV continous sedation	5	3
other	3	2
Unknown/missing	99	-
All procedures in same room*		
Yes	167	78
No	11	5
Unknown/missing	37	17
Each fraction planned*		
Yes	159	74
No	49	23
Unknown/missing	7	3

Abbreviations: HDR = high dose rate; ICBT = intracavitary brachytherapy; ICRU = International Commission on Radiation Units and Measurements; LDR = low dose rate, NSAIDs = nonsteroidal anti-inframmatory drugs.

* 215 patients treated with HDR-ICBT.

Table 4. Radiotherapy dose according to Fédération Internationale de Gynécologie Obstétrique stage

Dose (Gy)	Missing (n)	Stage I	Stage II	Stage III	Stage IVA	Total
EBRT						
Total point A dose						$p<0.001$
0–20	1	6 (18%)	5 (5%)	0	2 (6%)	13 (5%)
20–30	6	8 (24%)	19 (19%)	10 (8%)	3 (9%)	40 (14%)
30–40	3	10 (30%)	38 (38%)	65 (54%)	8 (24%)	121 (42%)
40–50	7	4 (12%)	19 (19%)	32 (27%)	7 (21%)	62 (22%)
50–60	2	5 (15%)	18 (18%)	12 (10%)	11 (34%)	46 (16%)
>60	0	0	0	1 (1%)	2 (6%)	3 (1%)
Missing	3	10	3	2	2	39
Median		30	30.6	34.9	41.1	32.4
Total point B dose						$p=0.0003$
0–20	0	2 (5%)	0	0	2 (6%)	4 (2%)
20–30	2	2 (5%)	1 (1%)	3 (3%)	2 (6%)	8 (3%)
30–40	1	3 (8%)	2 (2%)	5 (4%)	3 (9%)	13 (4%)
40–50	11	15 (38%)	35 (35%)	38 (31%)	7 (21%)	95 (32%)
50–60	5	17 (44%)	60 (60%)	72 (59%)	16 (49%)	165 (56%)
>60	0	0	2 (2%)	3 (3%)	3 (9%)	8 (3%)
Missing	3	4	4	1	2	31
Median		46.0	50.0	50.0	50.0	50.0
HDR-ICBT						
Total point A dose						$p=0.025$
0–10	0	0	2 (3%)	2 (2%)	1 (7%)	5 (2%)
10–20	3	5 (17%)	14 (18%)	34 (40%)	5 (36%)	58 (28%)
20–30	3	18 (62%)	49 (64%)	40 (47%)	6 (43%)	113 (54%)
30–40	0	2 (7%)	5 (6%)	1 (1%)	0	8 (4%)
>40	0	1 (3%)	0	0	0	1
Missing	4	3 (11%)	7 (9%)	8 (10%)	2 (14%)	24 (11%)
Median		23.1	22.0	20.0	20.0	20.3

Abbreviations: EBRT= external beam radiotherapy; HDR-ICBT= high dose rate intracavitary brachytherapy.

0–499 cGy (43/215, 20%), and 700–799 cGy (15/215, 7%). A single dose to point A over 8 Gy was applied only in two patients. The median number of HDR-ICBT insertions was 4 (range, 1–8). The median total dose of ICBT at point A was 20.3 Gy for HDR and 40.1 Gy for LDR. In cases of HDR-ICBT, total dose to point A decreased significantly with increasing stages. Median total dose of HDR-ICBT at point A was 23.1 Gy for Stage I, 22.0 Gy for Stage II, 20.0 Gy for Stage III, and 19.9 Gy for Stage IVA ($p = 0.025$). For calculation of total dose of EBRT and HDR-ICBT, biologically effective doses (BED) for tumor effect were calculated on the basis of $\alpha/\beta = 10$. The median total BED at point A was 74 Gy_{10} in cases treated with HDR-ICBT. There was no significant difference in total BED among the stages. Median total point A BED was 72 Gy_{10} for Stage I, 75 Gy_{10} for Stage II, 72 Gy_{10} for Stage III, and 77 Gy_{10} for Stage IVA ($p = 0.47$).

The median overall treatment time (OTT) was 47 days. OTT exceeded 8 weeks in 88 patients (28%).

Chemotherapy

Chemotherapy was applied in 104 patients (32%). Fifty-six patients (17%) were treated with concurrent chemoradiation (CCRT). Use of CCRT significantly varied according to FIGO stage ($p = 0.0039$). Chemotherapy was administered to 3 patients (7%) in Stage I, 12 patients (12%) in Stage II, 34 patients (28%) in Stage III, and 5 patients (14%) in Stage IVA. Neoadjuvant chemotherapy (NAC) before radiation therapy was given in 52 patients (16%).

DISCUSSION

This study describes the general patterns of radiotherapy practice for uterine cervical cancer from 1999 to 2001 in Japan. We examined the changes within Japan over the years and the differences in practice between Japan and the United States (Table 5).

External beam radiotherapy

For the radiation field (planning target volume [PTV]), almost all patients were treated with whole pelvic radiotherapy. Only a small number of patients received radiotherapy with an extended field including the para-aortic region. These results did not change over the years when comparisons were made with the previous JPCS (16). The U.S. PCS reported that only 11% of patients received extended field radiotherapy (12). Despite the positive results of the Radiation Therapy Oncology Group trial 79-20 (19), the standard PTV for EBRT in clinical practice in both Japan and the United States remained the whole pelvic region without para-aortic irradiation.

Table 5. Comparison of patterns of radiotherapy in cervical cancer patients between Japan and the United States

Parameters	Japan PCS 1995–1997*	Japan PCS 1999–2001	US PCS
Exrternal beam			
PTV			
Extended field	1%	3%	11%†
Beam energy			
Co60–9 MV	30%	26%	17%†
10–14 MV	57%	71%	19%†
15 MV≤	8%	3%	62%†
Technique			
Anteroposterior	95%	87%	19%†
Four-field box	2%	7%	80%†
Midline block			
Yes	69%	70%	6%†
Intracavitary brachytherapy			
Performed			
Yes	77%	82%	93%‡
Dose-rate			
LDR	8%	11%	78%‡
HDR	85%	89%	13%‡
Total dose to central tumor§ (median BED)	—	74 Gy_{10}	103 Gy_{10}‡
Overall treatment time (median)	49 days	47 days	57 days‡

Abbreviations: BED = biologically effective dose; LDR = low dose rate; HDR = high dose rate; PTV = planning target volume.
* Recalculated % including missing values.
§ point A dose (EBRT+HDR-ICBT).
† 1992–1994.
‡ 1996–1999.

As for beam energy, use of 9 MV or less decreased, and use of 10–14 MV increased (16). In the United States, the percentage of patients receiving 15 MV was largest (9, 12). The four-field technique was applied slightly more frequently in the present JPCS than the preceding JPCS (16). However, most patients were treated with the opposing AP-PA technique. In contrast, the four-field technique was applied in 80% of the patients in the United States (12). In the present survey, median isocenter depth of the AP-PA portals was 9 cm, indicating that the body thickness of females in Japan is small. Although there are no data, the body thickness is presumed to be larger in American patients compared with Japanese patients. Therefore, after taking body thickness into account, we thought that the beam energy and method of external beam radiotherapy used in Japan is appropriate. Even in Japanese patients whose body thickness is smaller than that of American patients, multiple field radiotherapy (*e.g.*, four-field) should be selected when a low-energy beam is used.

In this survey, a midline block was used in most patients, and no change in this practice was observed over the years (16). In contrast, the midline block was rarely used in the United States (12). The widespread use of the midline block was considered the result of following schedules specified in Japanese guidelines (7). One reason for less frequent use of the midline block in the United States may be the use of the four-field technique. Mell *et al.* (20) reported use of intensity-modulated radiation therapy (IMRT) in 27% of patients with gynecologic cancer in the United States. Because the use of IMRT could increase in Japan as well, it will be necessary to reexamine the advantages of using the midline block.

Intracavitary brachytherapy

The application rate of ICBT slightly increased compared with the previous PCS (16). However, the application rate was less in Japan than in the United States (12, 13). Intracavitary brachytherapy should be applied more routinely for patients treated by definitive radiotherapy in Japan. One fourth of the patients had received ICBT at another medical institution. In contrast, the percentage of such patients was reported as 8.5% in the United States (21).

HDR was used in approximately 90% of the patients, which was almost the same rate as that of the previous JPCS (16). In the United States, this rate was lower than that of Japan: 24% according to the ABS survey (1995) (22) and 16% according to the U.S. PCS survey (1996–1999) (21). We consider that the difference in the dose rate is one of the major differences between Japan and the United States. In the present study, the ICBT sources Co-60 and Ir-192 were used in roughly the same number of cases. The use of Ir-192 increased compared with the previous JPCS (16). In the early 2000s, the Japanese Society for Therapeutic Radiology and Oncology recommended the discontinuation of Co-60 as a remote afterloading brachytherapy source in Japan. The increase in the use of Ir-192 could be the result of compliance with this recommendation. Further increase in the use of Ir-192 and decrease in the use of Co-60 are expected in the next survey.

The ABS made a number of recommendations regarding HDR-ICBT techniques (5). The present study showed that analysis of the dose to organs at risk was performed in only a small percentage of patients. The doses were more often determined by using a dosimeter than the ICRU 38 reference point calculation. Sakata *et al.* indicated that the measured rectal dose significantly correlated with the incidence of rectal complications (23). In the United States, the practice of using a dosimeter for dosimetry has been called into question. The ABS recommended the use of the ICRU 38 reference point calculation (5). Many studies showed that late rectal complications can be predicted by the calculated doses at the ICRU 38 reference points (24, 25). According to the ABS survey, rectal/bladder doses are evaluated in 80% or more of patients at U.S institutions where HDR is performed (22).

The ABS also recommends conscious sedation for HDR-ICBT applicator insertions (5). However, it was surprising to discover that many patients in both the present and previous JPCS (16) received no pretreatment for HDR-ICBT applicator insertion. Intracavitary brachytherapy plays an important role in the radiotherapy of uterine cervical cancer. Accurate insertion can hardly be achieved if patients

Table 6. Standard radiotherapy schedule for uterine cervical cancer in Japan

FIGO stage	Central pelvic dose of EBRT (Gy)	Point A dose of HDR-ICBT (Gy/fc.)	Total BED at point A (Gy_{10})
I	0	29/5	46
II small	0	29/5	46
II large	20	23/4	60
III (small-medium)	20–30	23/4	60–72
III (large)	30–40	15/3–20/4	71–78
IVA	30–50	15/3–20/4	71–83

Abbreviations: BED = biologically effective dose; EBRT = external beam radiotherapy; FIGO = Fédération Internationale de Gynécologie Obstétrique; HDR-ICBT: high dose rate intracavitary brachytherapy.

experience discomfort. Therefore, we consider that pretreatment, such as conscious sedation, should be used for HDR-ICBT applicator insertion.

The single, total dose of HDR-ICBT was lower in the present study than the previous JPCS (16). The reason is unknown, but it might be related to an increase in the use of concurrent chemoradiotherapy (CCRT), which will is discussed subsequently.

Radiation dose

Table 6 shows the radiotherapy schedules indicated in the aforementioned general rules (7) and their biologically effective doses (BED) by stages. It also shows that the dose for the cervical tumor—namely, the total dose of EBRT and HDR-ICBT (point A dose)—increases with stage progression. In this present study, BED ranged from 72 to 77 Gy_{10} among the stages, indicating that differences among the stages were small. The schedules advocate the use of the midline block starting at 0–20 Gy of EBRT for Stages I and II. However, only 20% of patients followed the rule in this present study. Many other patients received EBRT exceeding these doses without the midline block. As a result, the total dose (EBRT+HDR-ICBT) to the central pelvis in early FIGO stages was higher than estimated. In contrast, treatment of patients in Stage III and IVA followed the schedules indicated in the general rules.

It was reconfirmed that the dose to uterine cervical tumors was lower in Japan than in the United States (25–27). The biologically effective dose (BED) of the schedules recommended by the ABS is approximately 100 Gy_{10} (5). In the United States PCS, the mean value of the linear quadratic equivalent dose was 85.5 Gy for patients treated using HDR-ICBT in 1996–1999 (21). When converted to BED, this value was 103 Gy_{10}. The difference in dose between Japan and the United States may be attributed to the difference in the standard schedules recommended in each country. The issue of dose range will need to be resolved before an international collaborative study can be initiated (8). The validity of each dose needs to be evaluated by outcome analysis.

Overall treatment time

Overall treatment time (OTT) is considered an important factor that affects the outcome of radiotherapy for uterine cervical cancer (28, 29). The ABS proposed that the OTT should be limited to within 8 weeks (5). The median OTT was shorter in this study (47 days) than in the previous JPCS (16). However, the OTT exceeded 8 weeks in almost 30% of patients. More effort to avoid treatment interruption to limit OTT within 8 weeks should be made. In the United States, the median OTT was reported to be 57 days (21). This difference between Japan and the United States may be due to differences in treatment schedules. In Japan, a midline block is inserted and ICBT starts in the middle of the EBRT treatment period.

Chemotherapy

In the present study, 32% of the patients received chemotherapy, indicating an increase from the previous JPCS (16). In particular, the rate of CCRT increased from 5% to 17% (16). The increase could be due to adoption of practices shown effective by RCTs published in 1999 (1–3). In the U.S. PCS (1996–1999), the percentage of patients who received chemotherapy was reported to be 19% in 1996, 28% in 1997, and 26% in 1998. However, it dramatically increased to 63% in 1999 (13). Further increase in the use of CCRT is expected in both Japan and the United States, and the monitoring of such changes should be continued.

Whereas several RCTs revealed negative therapeutic value of neoadjuvant chemotherapy (NAC) before radiotherapy in the mid-1990s, 16% of the patients were still treated with this strategy during this surveyed period. Surprisingly, the application rate was almost the same as that reported in the 1995–1997 JPCS survey (14%) (16). The usage of this strategy should be further monitored closely as well as CCRT.

Conclusions

We describe the status of definitive radiotherapy for uterine cervical cancer in Japan from 1999 to 2001. As in the previous survey (1995–1997), the EBRT conditions, such as the beam energy and technique of EBRT, were different between Japan and the United States. However, conditions of EBRT in Japan were becoming more standardized. For ICBT, aspects of the technique, such as dosimetry of organs at risk and supportive medication (*i.e.*, conscious sedation), can be improved. The total BED (EBRT + HDR-ICBT) delivered to the primary lesion in Japan was approximately 70% of that in the United States. The median OTT in Japan was approximately 80% of that in the United States. Compared with the previous JPCS, our study found that the use of CCRT has increased. This increase is considered to be due to the adoption of practices shown effective by RCT results published in 1999.

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CLINICAL INVESTIGATION **Lung**

CHANGES IN PATTERNS OF CARE FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS OF THE 99-01 PATTERNS OF CARE STUDY—A NATIONWIDE SURVEY IN JAPAN

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Background: This study was undertaken to analyze the practice process of thoracic radiotherapy (TRT) and evaluate changes in patterns of care for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan.
Methods and Materials: The Patterns of Care Study (PCS) conducted the second nationwide survey of care process for patients with LS-SCLC treated by using TRT between 1999 and 2001.
Results: The PCS collected data for 139 patients with LS-SCLC (man-woman ratio, 5:1; median age, 69 years; age > 70 years, 43%; Karnofsky Performance Status > 70, 73%; and Stage III, 88%). Median total dose was 50 Gy. Twice-daily TRT was used in 44% of patients. Median field size was 12 × 14 cm. The most commonly used photon energy was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV comprised 12%. Three-dimensional conformal therapy was used with 12% of patients. Computed tomography simulation was performed in 40% of cases. Only 12 patients (8.6%) received prophylactic cranial irradiation (PCI). Concurrent chemotherapy and TRT (CCRT) was used for 94 patients (68%). Only 6 patients (4.4%) entered clinical trials. Compared with the previous PCS 95-97, significant increases in the use of CCRT (34–68%; $p < 0.0001$), twice-daily TRT (15–44%; $p < 0.0001$), and PCI (1.7–8.6%; $p = 0.0045$) were observed, although the absolute number of patients receiving PCI was still extremely low.
Conclusions: Evidence-based CCRT and twice-daily TRT has penetrated into clinical practice. However, PCI is not yet widely accepted in Japan. © 2008 Elsevier Inc.

Patterns of Care Study, Small-cell lung cancer, Thoracic radiation therapy, Nationwide survey, Practice process.

INTRODUCTION

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice processes for selected malignancies during a specific period (1). In addition to documenting practice processes, the PCS is important in developing and spreading national guidelines for cancer treatment. In Sept 1998, the Japanese PCS conducted the first nationwide survey for patients with lung cancer treated using thoracic radiotherapy (TRT) between 1995 and 1997 (PCS 95-97). The main findings from the PCS 95-97 are summarized as follows. First, the use of TRT for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan is predominantly influenced by institutional characteristics, rather than age group. Second, patient age significantly influenced the use of chemotherapeutic modality, such as etoposide and cisplatin for patients with LS-SCLC (2, 3).

Because results of several key clinical studies of patients with LS-SCLC were reported between 1997 and 1999, it seems meaningful to evaluate whether practice processes in Japan were changed accordingly. The second PCS for lung cancer investigated patient characteristics, workup studies, the process of TRT, and use of chemotherapy in patients with LS-SCLC treated by using TRT between 1999 and

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2001. The objectives of the present study are as follows. First, compile processes in TRT for patients with LS-SCLC treated between 1999 and 2001, and second, compare patient characteristics and treatment modalities between the PCS 95-97 and PCS 99-01 in Japan.

METHODS AND MATERIALS

Between July 2002 and August 2004, the PCS conducted a second national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format for patients with lung cancer. The PCS performed an extramural audit survey for 73 (38 academic and 35 nonacademic institutions) of 556 institutions by using stratified two-stage cluster sampling and collected data for 768 eligible patients with lung cancer. Data collection consisted of two steps of random sampling. Before random sampling, all institutions were classified into one of four groups. Criteria for stratification were described elsewhere (2, 4). Briefly, the PCS stratified Japanese institutions as follows: A1, such academic institutions as university hospitals or national/regional cancer center hospitals treating 430 or more patients per year; A2, academic institutions treating fewer than 430 patients; B1, nonacademic institutions treating 130 or more patients per year; and B2, those treating fewer than 130 patients per year. Cutoff values for numbers of patients treated per year between A1 and A2 institutions and B1 and B2 institutions were increased from those used in the previous PCS because of the increase in number of patients treated using radiation therapy in Japan (4).

Eligible patients included those with 1997 International Union Against Cancer Stages I–III lung cancer treated by using TRT between 1999 and 2001, with Karnofsky Performance Status (KPS) greater than 50 before the start of treatment and no evidence of other malignancies within 5 years. The International Union Against Cancer staging system was used because the PCS comprehensively surveyed patients with non-SCLC and those with SCLC. As mentioned, Stages I–III SCLC do not precisely match the definition of LS-SCLC by Mountain (5). However, no definition of this term has been universally accepted. The PCS survey of TRT charts showed that for patients with SCLC, the tumor could be encompassed within the TRT field. Thus, in the present study, all patients were regarded as having LS-SCLC.

The aims of this study are to provide patterns of practice concerning: (*1*) patient background; (*2*) workup studies; (*3*) TRT, including photon energies, total dose, spinal cord dose, field arrangements, prescription point, and use of prophylactic cranial irradiation (PCI); and (*4*) chemotherapy, including agents, number of chemotherapy cycles, sequence of chemotherapy, and TRT. Patient background included demographics and medical status, such as KPS, comorbidities, stage, and whether treated on an outpatient basis. In addition, practice patterns of the PCS 99-01 were compared with those of the PCS 95-97.

To validate the quality of collected data, the PCS used the Internet mailing list among all the surveyors. *In situ* real-time check and adjustment of the data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data unknown. We combined missing and unknown in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with unknown values were included when both percentage and significance values were calculated. Statistical significance was tested by using chi-square test. A $p < 0.05$ was considered statistically significant. Overall survival, assessed from the first day of radiation therapy, was estimated by using the Kaplan-Meier product-limit method, and differences were evaluated using log-rank test.

RESULTS

Patient backgrounds

There were 141 patients with SCLC, which constituted 18% of all patients with lung cancer surveyed. Of those, 2 patients underwent initial surgical resection and adjuvant postoperative irradiation. Thus, in the present study, the PCS analyzed the remaining 139 patients who did not undergo surgery (Table 1).

There were 116 men and 23 women with an age range of 36–85 years (median, 69 years). Patients older than 70 years constituted 43% of the patient population. For that elderly patient pool, the institutional breakdown was as follows: 31% in A1, 39% in A2, 50% in B1, and 50% in B2 ($p = 0.037$). For comorbidities, the most frequent adverse medical conditions were cardiovascular disease (34%) and diabetes (14%). Seventy-three percent had KPS of 80% or greater. Comparison of four institutional groups failed to show differences in terms of patient background other than patient age and KPS. Patients with KPS of 80 or greater comprised 89% of A1, 55% of A2, 74% of B1, and 65% of B2 strata ($p = 0.0071$). A majority of patients (88%) had Stage III disease. There were no significant differences in distributions of T and N classifications or clinical stages between institutional groups. Only 5% of all patients were treated on an outpatient basis.

Workup studies

Workup studies are listed in Table 2. Pretreatment workup included chest computed tomography (CT) in 96%, bronchoscopy in 93%, brain CT or magnetic resonance imaging in 86%, and bone scan in 79% of surveyed patients. Chest/abdominal CT and bone scan were used for a majority of patients, whereas positron emission tomography (PET) was used for an extremely small number of patients. Comparison of four institutional groups failed to show differences in terms of workup studies.

Practice process of TRT

Thoracic radiotherapy methods are listed in Table 3. Median total dose of TRT was 50 Gy, and median field size was 12 × 14 cm. Median dose to the spinal cord was 42 Gy. A CT simulator was used for planning in 40% of patients. Three-dimensional conformal therapy was used in 12%. The planning target volume included the ipsilateral hilus in 96%, ipsilateral mediastinum in 96%, contralateral mediastinum in 84%, contralateral hilus in 17%, ipsilateral supraclavicular region in 25%, and contralateral supraclavicular region in 15%. Field reduction during the course of TRT was done for 61%. Twice-daily radiotherapy was used for 44%. Photon energy generally was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV were used for 12%. Only 12 patients (8.6%) received PCI. Median dose of PCI was 25 Gy. Only 6 patients (4.4%) entered clinical trials.

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions A1	A2	B1	B2	Total	*p*-value
No. of patients	36	23	54	26	139	
Age (y)						0.037
Range	44–85	36–81	40–81	54–85	36–85	
Median	69	68	71	71	69	
>70 (%)	31	39	50	50	43	
Sex						0.780
Men	30	18	47	21	116	
Women	6	5	7	5	23	
Karnofsky performance status						0.013
≥80 (%)	89	55	74	65	73	
Clinical stage/UICC 1997						0.475
I	0	1	2	2	5	
IIA, IIB	3	3	4	1	11	
IIIA	10	6	19	10	45	
IIIB	23	13	28	13	77	
Unknown/missing	0	0	1	0	1	
T classification						0.569
T1–2	14	11	25	14	64	
T3–4	22	12	28	12	74	
Unknown/missing	0	0	1	0	1	
N classification						0.551
N0–1	7	4	9	6	26	
N2–3	29	19	44	20	112	
Unknown/missing	0	0	1	0	1	

Abbreviation: UICC = International Union Against Cancer.

Institutional stratification influenced several radiotherapeutic parameters (Table 4). Photon energy of 6 MV or greater was used for 97% of patients in A1, 96% in A2, 87% in B1, and 69% in B2 institutions ($p = 0.0006$). The ^{60}Co machines were not used in any A1 to B1 institutions. Twice-daily radiotherapy was used for 57 of 113 patients in A1 to B1 institutions, but only 4 of 26 patients in B2 institutions were treated in that manner ($p = 0.0012$). The PCI was used for 7 of 36 patients (19%) in A1 institutions, but only 5 patients (4.9%) in the remaining institutions ($p = 0.0073$). Use of a CT simulator was more frequent in A1 (52%) and A2 (65%) compared with B1 (34%) and B2 (17%) institutions ($p = 0.011$).

One hundred twenty-nine patients (93%) received systemic chemotherapy. Of those, platinum-based chemotherapy constituted 98%. Concurrent chemotherapy and TRT (CCRT) was used for 68% (73% of patients who received systemic chemotherapy). Median number of chemotherapy cycles was four. Median times from the first day of systemic chemotherapy to the first date and last date of TRT were 3 and 44 days, respectively. Proportions of patients who received chemotherapy were 97% in A1, 96% in A2, 91% in B1, and 89% in B2 institutions ($p = 0.49$).

Comparison between two PCS studies

Patient backgrounds and practice patterns in PCS 99-01 were compared with those in PCS 95-97. Differences between the two studies are listed in Table 5. Based on two-stage cluster sampling, the ratios of academic to nonacademic institutions were almost equal in the two surveys. Although median age in PCS 99-01 was slightly older than that in PCS 95-97, patients' backgrounds were similar in the studies. Use of obsolete treatment equipment (photon energy < 6 MV and ^{60}Co) decreased from 20% in PCS 95-97 to 12% in PCS 99-01 ($p = 0.06$). The greatest differences were seen in the use of twice-daily TRT and CCRT. Twice-daily TRT increased from 15% in PCS 95-97 to 44% in PCS 99-01 ($p < 0.0001$). Use of CCRT in PCS 99-01 was twice as high as in PCS 95-97 (68% vs. 34%; $p < 0.0001$). Although a significant increase in the use of PCI was observed (1.7–8.6%; p = 0.0045), the rate was still extremely low in Japanese practice.

Table 2. Percentage of patients examined by using each diagnostic technique in the course of staging

Chest CT	96%
Chest MRI	7%
Bronchoscope	93%
Bone scan	79%
Abdominal CT	88%
Positron emission tomography	2%
Brain CT or MRI	86%

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.

Table 3. Process of thoracic radiation therapy for patients with limited-stage small-cell lung cancer

Median total dose (Gy)	50
Median spinal cord dose (Gy)	42
Use of CT simulator (%)	40
Three-dimensional conformal therapy (%)	12
Beam energy (%)	
^{60}Co	1.4
<6 MV	10.8
≥6 MV	88
Median field size (cm)	12 × 14
Field reduction during treatment (%)	61
IRB-approved protocol treatment (%)	4.4
Twice-daily radiotherapy (%)	44
Prophylactic cranial irradiation (%)	8.6
Area included in planning target volume (%)	
Ipsilateral hilus	96
Ipsilateral mediastinum	96
Contralateral mediastinum	84
Contralateral hilus	17
Ipsilateral supraclavicula	25
Contralateral supraclavicula	15
Systemic chemotherapy (%)	93
Concurrent chemotherapy and thoracic radiotherapy (%)	68

Abbreviations: CT = computed tomography; IRB = institutional review board.

Comparison of preliminary outcomes between studies

There are known limitations in survival analyses in this type of retrospective survey study. Still, preliminary outcome data in the two studies could be compared. Overall survival rates of the entire patient pool in each study are shown in Fig. 1. Two-year survival rates in PCS 95-97 and PCS 99-01 were 34% and 45%, with a median follow-up of only 11 months in both studies, respectively. Median survival times of the patient pools in PCS 95-97 and PCS 99-01 were 14 and 17 months, respectively. These differences did not reach a statistically significant level.

Table 4. Process of thoracic radiation therapy influenced by institutional stratification

	Stratification of institutions					
Characteristics	A1	A2	B1	B2	Total	*p*-value
Photon energy						0.0006
^{60}Co	0	0	0	2	2	
<6 MV	1	1	7	6	15	
≥6 MV	35	22	47	18	122	
Twice-daily fractionation used						0.0012
Yes	18	11	28	4	61	
No	18	12	26	22	78	
Treatment planning						0.011
Use of CT simulator (%)	52	65	34	17	40	
Prophylactic cranial irradiation used						0.0002*
Yes	7	2	3	0	12	
No	29	17	48	24	118	
Unknown/missing	0	4	3	2	9	

Abbreviation: CT = computed tomography.
* A1 vs. A2–B2; $p = 0.0073$.

Table 5. Comparison of treatment modalities between two studies

Background and treatment process	PCS 95-97 (n = 174)	PCS 99-01 (n = 139)
SCLC/all lung cancer (%)	16	18
Median age (y)	65	69
KPS > 70 (%)	70	73
Stage III (%)	87	88
Median total dose (Gy)	50	50
Photon energy <6 MV or ^{60}Co (%)	20	12
Use of CT-simulator (%)	NA	40
Twice-daily thoracic radiotherapy (%)*	15	44
Chemotherapy used (%)	92	93
Concurrent chemoradiation (%)†	34	68
Prophylactic cranial irradiation (%)‡	1.9	8.6
Survival at 2-years (%)	34	45

Abbreviations: PCS = Patterns of Care Study; SCLC = small-cell lung cancer; KPS = Karnofsky Performance Status; CT = computed tomography; NA = not available.
* $p < 0.0001$ by chi-square test.
† $p < 0.0001$ by chi-square test.
‡ $p = 0.0045$ by chi-square test.

DISCUSSION

Results of the present PCS reflect national treatment trends for TRT for patients with LS-SCLC in Japan between 1999 and 2001. Through this second nationwide audit survey and data analysis, PCS established the general patterns of care for patients with LS-SCLC in Japan. Results also show the influence of the structure of radiation oncology on the process of TRT and how state-of-the-art cancer care supported by clinical trial results has penetrated into the national practice process during the study period.

During the study period, TRT for LS-SCLC constituted less than one fifth of all radiation therapy for patients with lung cancer. This result was similar to data from the United States (6). Use of such staging studies as chest CT, bone scan, and PET scan for patients with SCLC was in line with guidelines (7) and very similar to the report from the United States (6). A PET scan in clinical use was still scarce. Only a small fraction of patients participated in clinical trials similar to those observed in the United States. In Japan, twice-daily TRT was used more frequently and PCI was used less frequently compared with the United States. However, it should be noted that subjects of the PCS in the United States were treated between 1998 and 1999, preceding the results of key studies that supported the use of twice-daily radiation therapy and PCI.

The study shows that more suitable photon energies were used in TRT at academic institutions. Thirty-one percent of patients in B2 institutions were treated with a linear accelerator with less than 6 MV or a ^{60}Co machine that did not meet the standard of care for equipment to treat patients with lung

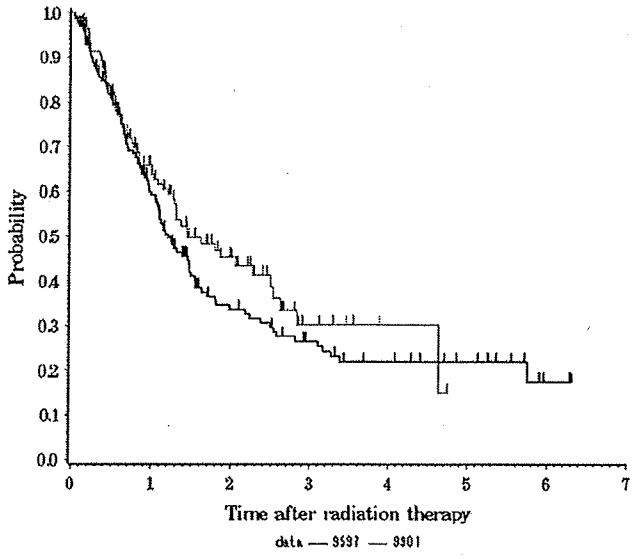

Fig. 1. Kaplan-Meier estimate of overall survival of patients with Stages I–III small-cell lung cancer surveyed in the 1995–1997 (dark line) and 1999–2001 (bright line) Patterns of Care Studies in Japan.

cancer, although this rate decreased from PCS 95-97 (>40% in B2) and was somewhat favorable compared with postoperative radiation therapy for patients with lung cancer in the same period (8). The availability of CT simulators was greater than 50% in academic institutions, but only one third in B1 and even lower in B2 institutions. In modern radiation therapy, CT-based treatment planning is essential for TRT to achieve optimal target coverage while reducing the dose to normal tissue. Twice-daily TRT was used more frequently for patients in A1 to B1 institutions than patients in B2 institutions. The PCI was used for 19% of patients in A1 institutions, but only 4.9% of patients in the remaining institutions. Although the general quality of radiation oncology improved from PCS 95-97, results of the present study show that institutional stratification still influences the structure and process of radiotherapy, such as availability of CT simulators, the flexibility of external beam energy selection, and use of evidence-based cancer care in Japan.

During the past 20 years, survival prolongation in patients with LS-SCLC was attained mainly by clinical trials that studied some aspect of radiation therapy, such as integration of TRT (9, 10), optimization of timing and fractionation of TRT (11), and introduction of PCI (12). The TRT is an essential component of the standard management of patients with LS-SCLC. Two meta-analyses showing the advantage of the addition of TRT to systemic chemotherapy, published in 1992 (9, 10), preceded our first national survey (PCS 95-97). In PCS 99-01, although 43% of all surveyed patients were older than 70 years and 23% of all patients had KPS of 70% or less, 93% of all patients received chemotherapy. This percentage is very similar to that in PCS 95-97 (2, 3).

When interpreting our data, it is important to note that they are limited to patients who received TRT as part of their overall treatment regimen. However, these two surveys showed that use of systemic chemotherapy was reasonably high in Japanese practice. Based on several studies published during the past 10 years, CCRT up front has emerged as a standard of care generating the highest survival rates (11, 13, 14). A landmark study supporting twice-daily TRT was published in 1999 after the previous PCS 95-97 (11). In that study, Turrisi *et al.* (11) showed a significant benefit in 5-year survival rate with the use of twice-daily TRT (45 Gy in 1.5 Gy fractions twice daily) concurrent with chemotherapy compared with once-daily TRT (45 Gy in 1.8 Gy fractions every day). Use of CCRT in PCS 99-01 (68%) was twice as high as in PCS 95-97 (34%). Similarly, there was a notable increase in the use of twice-daily TRT after PCS 95-97. In the present study, 44% of patients received twice-daily TRT, nearly three times as high as in PCS 95-97. Although it is still unclear whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose of 60–70 Gy delivered by using more standard fractionation, it seems that diffusion of twice-daily TRT to Japanese practitioners was rapid. It seems likely that the marked increase in use of twice-daily TRT with concurrent chemotherapy in Japan contributed to the widespread use (95%) of inpatient treatment in PCS 99-01. In general, once-daily treatment is better accepted for outpatient care, whereas twice-daily scheduling is convenient for the care of inpatients, but at greater cost. Marked increases in the use of CCRT and twice-daily TRT indicates greater acceptance of these treatment modalities by radiation oncologists across Japan.

However, PCI has yet to be systematically adopted in Japanese practice. Despite the 1999 publication of another landmark trial that showed the survival advantage of PCI for complete responders (12), only 8.6% of all patients received this intervention. At the time of PCS 95-97, the role of PCI had not been established and it was used for only 1.9% of all patients (2). Before the present survey, it was expected that the percentage of patients who received PCI would be greater on the basis of the meta-analysis. Although a slight increase in use of PCI was observed, the rate was still extremely low in Japan. Information about the number of complete responders was outside the audit. However, a complete response rate of at least 50% is expected for study subjects (15). Whether this is caused by the small number of radiation oncologists in Japan or the small number of patients who received radiation therapy for cancer treatment is unknown. We reported previously that the number of full-time radiation oncologists is low, especially in nonacademic institutions in Japan (2). According to cancer statistics in Japan, radiation therapy was used for only 11.3% of all patients with cancer in 1999 compared with medical (27.5%) and surgical treatment (69.9%) (16). It is not clear why evidence-based PCI has not yet been widely accepted in Japan as opposed to the rapid diffusion of CCRT and twice-daily TRT in clinical practice. It appears that physicians in Japan hesitate to use PCI, and their patients are reluctant to receive PCI even if it is beneficial. Results of the ongoing third national survey in Japan will be particularly interesting in this regard.

Nonsignificant survival improvement in patient outcome was observed between PCS 95-97 and PCS 99-01. The current PCS has limitations in terms of outcome analysis because of a short follow-up period, significant variations in follow-up information according to institutional stratification (4, 17), and difficulties in outcome survey. One of the ultimate goals of the PCS is to determine how structure and processes of radiation therapy affect patient outcomes, including local control, survival, and quality of life. However, since 2006, personal information is strictly protected by law and outcome surveys are difficult to perform in Japan, even for patients with cancer. Cancer is not yet a reportable disease in Japan. Currently, limitations in data accumulation concerning patient outcomes in this type of survey encouraged us to develop new health care data collection systems and linkages among systems that make systematic recording and analysis of structure/process and outcome data part of routine quality monitoring (Japanese National Cancer Database, funded by the Ministry of Health, Labor, and Welfare Japan).

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Original Article: Clinical Investigation

Ten year trend in prostate cancer screening with high prostate-specific antigen exposure rate in Japan

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Background: The tendency of the results and quality control of prostate cancer screening serially performed for 10 years in an area of Japan were evaluated.

Methods: A total of 39 213 men over 55 years of age have participated in the mass screening of prostate cancer in the Otokuni District, since 1995. Men whose prostate-specific antigen (PSA) levels were more than 4.1 ng/mL were indicated for the second screening. In the second screening, prostate-specific antigen density (PSAD) was calculated in men whose PSA levels ranged from 4.1 to 10.0 ng/mL.

Results: Secondary screening was indicated in a total of 2428 subjects, of whom 1633 underwent it. Prostate cancer was diagnosed in 267 men. As a result of the evaluation of the indication of prostate biopsy according to the PSAD in 894 who underwent secondary screening for the first time, the procedure was judged to be unnecessary in 269 (35%) of 765 cases. Of these 269 subjects, 23 (8.5%) were found to have cancer. Clinically localized prostate cancer increased by 17%, and locally advanced and metastatic cancers decreased by 12% in the second compared with the first five years of the ten-year period. The exposure rate of PSA screening in the Otokuni District was 65% with the application for the rate of screenees whose PSA level was 4.1 ng/mL or above.

Conclusions: The Japanese basic health screening system allows the determination of high-PSA exposure areas. Serial prostate cancer screening showed a tendency of stage migration in the screened cancer patients. The use of PSAD in secondary screening substantially reduces the necessity of prostate biopsy; however, the encouragement of PSA-positive individuals to periodically receive prostate cancer screening is essential to maintain the quality of the screening system.

Key words: Prostate cancer, PSA, screening, PSA density

Introduction

The incidence of and mortality from prostate cancer in Japan is still lower than it is in Western countries.[1] However, prostate cancer is becoming a major public health concern in Japan. The age-adjusted incidence of this malignancy rapidly increased 6.5 times between 1975 and 1998.[2] In addition, the age-adjusted mortality rate also increased 4.3 times between 1980 and 2000.

In conjunction with the recent rapid increases in the incidence of and mortality from prostate cancer in Japan, the percentage of local governments providing prostate cancer screening increased five times during the six years following 2000 (14.7% in 2000, 71.2% in 2006).[3] This rapid increase in the number of local governments that started prostate cancer screening reflects the recent increase in concern over prostate cancer among the Japanese.

In Japan, the execution of prostate cancer screening is left primarily to local health administrative organizations, university and core hospitals, medical societies mostly consisting of local practitioners, and public or private screening institutions. A survey of such screening facilities in 2006 showed that 87% of them were local health administrative organizations.[3] However, in executing prostate cancer screening in urban areas, the efforts of local health administrative organizations alone are insufficient to efficiently attract primary screenees, and the involvement of general practitioners, most of whom are family physicians, in primary screening is necessary. Also, the designation of core hospitals for secondary screening is necessary for physicians who perform prostate needle biopsy to be able to carry out the detailed management of databases. In Japan, basic health screening consisting of inquiries, body measurements, percussion and auscultation, sphygmomanometry, blood chemistry tests, diabetes tests, and electrocardiogram (ECG) is widely available for people aged 40 years and above as an elderly health protection measure for the promotion of the correct understanding of lifestyle-related diseases and their early detection and treatment.[4] In 1995 in the Otokuni District of Kyoto, we first established a primary prostate cancer screening system in which screenees can freely choose between screening by local governmental administration and individual screening at private medical facilities (primarily local clinics) cooperating in basic health screening. The objectives of this study were to examine Japan's original health screening system and to clarify the characteristics of prostate cancer patients detected by screening using the PSA density (PSAD) as an indicational criterion for prostate biopsy during the past 10 years. In addition, we tried to calculate the exposure rate of PSA screening in the Otokuni District.

Methods

The Otokuni District is located to the south of Kyoto City and consists of two cities and one town (Nagaokakyo City, Muko City, and Oyamazaki Town). It has a population of 147 500 (2004), of which 22 705 (2004) are males aged 55 years and over. The subjects of this study were those who desired screening for prostate cancer among the males aged 55 years and over who have undergone basic health screening in September to October each year since 1995. Primary screening was made by the examination of the serum PSA level alone with a cut-off level of 4.0 ng/mL. The serum PSA level was determined using a Delfia PSA assay kit in all subjects.

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Table 1 Prostate biopsy criteria of second screening

4.1 ≤ PSA ≤ 10	
– DRE-positive or TRUS-positive	Biopsy
– Both DRE and TRUS-negative	
– PSAD > 0.15	Biopsy
– PSAD ≤ 0.15	Recommend to undergo screening next year
PSA ≥ 10.1	Biopsy

DRE, digital rectal examination; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; TRUS, transrectal ultrasonography.

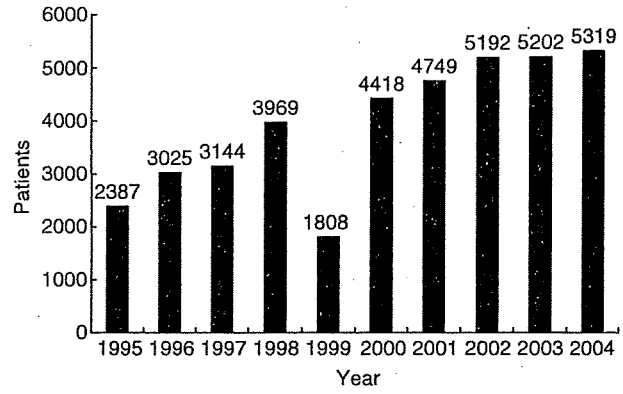

Fig. 1 Annual changes in the number of screenees.

The health administrative organization or private medical facilities in the Otokuni District informed the screenees in whom the serum PSA level was 4.1 ng/mL or above that they should receive secondary screening at a core hospital (Kyoto Saiseikai Hospital). The second screening including prostate biopsy was performed by urologists in Kyoto Saiseikai Hospital using the health insurance system. Table 1 shows the secondary screening system for the selection of candidates for prostate needle biopsy at the core hospital. Biopsy was indicated according to the PSAD, because it was reported to be promising as an indicator of prostate needle biopsy in individuals with a gray-zone PSA level (4.1–10.0 ng/mL) by a study team on the validity of mass screening for prostate cancer (Watanabe Team) under the Ministry of Health and Welfare (presently Ministry of Health, Labor and Welfare).[5]

Digital rectal examination (DRE) was performed by one urologist (K.K) who was a voting member of the Japanese Urological Association. Transrectal ultrasound sonography of the prostate was examined using an ultrasound machine equipped with a chair-type scanner (SSD-520, Aloca, Tokyo, Japan), and the prostate volume was obtained by the step-sectioned method. PSA density was calculated as PSA (ng/mL)/prostate volume (ml).[6] The cut-off value was defined as 0.15.

In men who were indicated for prostate biopsy, transperineal prostate biopsy was undertaken under local anesthesia. The sextant systematic biopsy (SSB) technique was applied between 1995 and 2001. Since 2002, in addition to the SSB technique, an additional sample has been taken from the far lateral region in each lobe. The clinical stage was evaluated according to the TNM system.[7]

Results

Figure 1 shows annual changes in the number of prostate cancer screenees. The number increased more than two-fold in 2004 compared with 1995, when prostate screening was started. In 1999, the number of screenees decreased, because only mass screening was performed; individual screening could not be performed because of the lack of cooperation by the local medical society.

A total of 39 213 people attended primary screening using PSA testing during the 10 years between 1995 and 2004. Of these screenees, 8420 (21%) underwent mass screening at health administration organizations in the Otokuni District, and 30 793 (79%) underwent individual screening at private medical facilities. The serum PSA concentration was 4.1 ng/mL or above in 2428 (6%) of all screenees. Of these screenees, 1633 (67%) received secondary screening, and prostate cancer was detected in 267. Of the 1633 secondary screenees, 1439 (88%) were examined at Kyoto Saiseikai Hospital regarding whether or not they should undergo prostate biopsy. Table 2 shows the percentage of the secondary screenees who underwent biopsy on the basis of their PSA level, the number of biopsies performed and the number of cancers detected (Table 2a: Initial screenees only. Table 2b: All secondary screenees). Of the screenees eventually diagnosed with cancer, 248 were diagnosed at Kyoto Saiseikai Hospital.

As previously described, the PSAD was calculated to determine the necessity of prostate biopsy. The serum PSA level was 4.1–10.0 ng/mL in 86% of the first-time screenees. Of these screenees, the PSAD > 0.15 or DRE was positive in 496 (65%), of whom prostate needle biopsy was performed in 482 (98%). In the screenees who underwent prostate needle biopsy, cancer was detected in 24% (118/487) and 52% (65/124) of those in whom the PSA level was 4.1–10.0 ng/mL and 10.1 ng/mL or higher, respectively. Of the 269 screenees in whom biopsy was not indicated based on the PSAD in the initial secondary screening (Fig. 2), 147 underwent secondary screening again, and prostate cancer was detected in 23.

The serum PSA level was 4.1–10.0 ng/mL in 83% (1193/1439) of all who underwent secondary screening. Of these screenees, biopsy was indicated in 704 (59%) but not in 489 (41%), because no abnormality was noted during DRE, and the PSAD was 0.15 or less. Eventually, biopsy was performed in 665 (94%) of these 704 screenees, and prostate cancer was diagnosed in 151 (23%, 151/665). Of the screenees in whom the PSA level was 10.1 ng/mL or higher, prostate cancer was detected in 43% of those who underwent biopsy. Two screenees who showed a PSA level of 4.0 ng/mL or less underwent secondary screening with prostate needle biopsy, because their PSA level had been 4.1 ng/mL or higher in the past, but were thereafter excluded from prostate needle biopsy as no sign of malignancy was noted. Three screenees who showed a PSA level of 10.1 ng/mL or higher but were judged not to have an indication for biopsy had also undergone prostate needle biopsy in the past.

Table 3 shows the age distributions of all those who underwent secondary screening ($n = 1439$; 55–96 years; median, 71 years) and those in whom cancer was detected ($n = 248$; 55–92 years; median, 72 years) at Kyoto Saiseikai Hospital. In both groups, a peak was observed at 70–74 years, and 28% and 29% of the respective groups belonged to this age level. Table 4 shows the distribution of clinical stages in the screenees who were found to have cancer at Kyoto Saiseikai Hospital ($n = 248$). The disease in 193 (78%) of these patients was clinically localized prostate cancer (T1c-T2bN0M0). In particular, the percentage of patients with clinically T1cN0M0 cancer increased two-fold in the second five years compared with the first. The patients with locally advanced cancer (T3N0M0) numbered 35 (14%) and patients with metastatic cancer comprised 13 (5%) over the whole period.

Table 2 Frequency of patients with indications of biopsy, number of biopsies performed, and number of cancers detected according to the PSA level in those who underwent secondary screening

PSA(ng/ml)	No. of patients	Biopsy indicated	Biopsy not-indicated	Biopsied	Cancers
2-a First-time secondary screenees only					
4.1–10	765	496	269	482	118
10.1–	129	129	0	124	65
Total	894	625	269	606	183
2-b All secondary screenees					
≤4.0	2	0 (0%)	2 (100%)	0 (0%)	0 (0%)
4.1–10	1193	704 (59%)	489 (41%)	665 (56%)	151 (13%)
10.1–	243	240 (99%)	3 (1%)	223 (92%)	97 (43%)
Lack of PSA	1	0	1 (100%)	0	0
Total	1439	944 (66%)	495 (34%)	888 (62%)	248 (17%)

PSA, prostate-specific antigen.

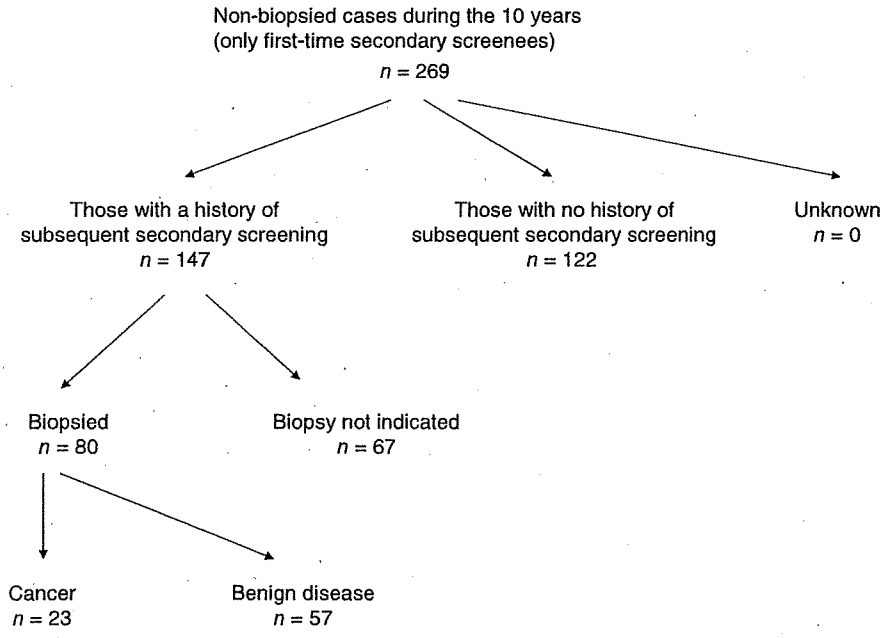

Fig. 2 Results of the follow-up of screenees in whom prostate needle biopsy was not conducted in secondary screening.

Although the ratio of clinically localized prostate cancer was 68% and the ratios of locally advanced cancer and metastatic cancer were both 27% from 1995 to 1999, the ratio of clinically localized prostate cancer between 2000 and 2004 increased by 15%, while that of locally advanced cancer and metastatic cancer within the same period decreased by 12%.

In this study, we calculated the total number of those who underwent primary screening during the 10-year period but could not calculate the number of those who were screened for the first time, because there was no system to discriminate first-time screenees and repeaters between 1995 and 1998. Therefore, the cancer detection rate in the true number of primary screenees cannot be calculated. In the Gunma Prefecture, in which prostate cancer screening has been performed annually for more than 10 years, the cancer detection rate was 1.13% (440/38 861).[8] To calculate the exposure rate of PSA screening in the Otokuni District, we tired to apply the detection rate of prostate cancer screening in the Gunma Prefecture. If the cancer detection rate in our study is assumed to have been similar to that in Gunma, the true number of primary screenees is estimated from the number of screenees in whom cancer was detected (267) to have been 23 628 (267/0.0113). Since the population of the Otokuni District aged 55 years and over was 22 705 in 2004, as mentioned above, all residents of the target population in this district are considered theoretically to have attended prostate cancer screening. This estimation may, of course, change with the method for the selection of candidates for secondary screening including the cut-off PSA levels for different age levels[9] and methods of prostate needle biopsy. Consequently, we tried to calculate the exposure rate of PSA screening using another method. In this study, the PSA level is considered to have been 4.1 ng/mL or above in 6.1% of all primary and secondary screenees during the 10-year period combined, and this value, calculated from the total number of screenees, is considered to reflect the true number of people with an abnormal PSA level in the Otokuni District. Therefore, of the 22 705 males aged 55 years and over in the Otokuni District, the PSA level is considered to be abnormal in

Table 3 Age distribution of those who underwent secondary screening ($n = 1439$) and those in whom cancer was detected ($n = 248$) at a core hospital

Age	Second screening	Cancer (detection rate)
55–59	32	10 (31%)
60–64	185	21 (11%)
65–69	378	52 (18%)
70–74	407	71 (17%)
75–79	243	45 (19%)
80–84	131	38 (29%)
85–89	47	8 (17%)
90–	16	3 (19%)
Total	1439	248
Mean ± SD	71.5 ± 7.0	72.5 ± 7.2
Median	71 years	72 years

SD, standard deviation.

Table 4 Distribution of clinical stages in the five-year periods of 1995–1999 and 2000–2004

Clinical stage	1995–1999	2000–2004	Total
T1cN0M0	23 (26%)	86 (54%)	109 (44%)
T2aN0M0	23 (26%)	31 (19%)	54 (22%)
T2bN0M0	14 (16%)	16 (10%)	30 (12%)
Sum of clinically localized cancer (T1c-2bN0M0)	60 (68%)	133 (83%)	193 (78%)
T3N0M0	17 (19%)	18 (11%)	35 (14%)
TxN1M0	0 (0%)	2 (1%)	2 (1%)
TxNxM1	7 (8%)	4 (3%)	11 (4%)
Unknown	4 (5%)	3 (2%)	7 (3%)
Total	88	160	248

1385 (22 705 × 0.06), since the number of those who were screened for the first time at the core hospital for secondary screening or other facilities was 903 men. In results, 65% (903/1385) of the target population in the Otokuni District is estimated to have undergone the PSA test.

Discussion

Basic health screenings are undertaken by a higher percentage of the population than other screening systems, and the percentage in the Otokuni District, Kyoto Prefecture (54.6%, 1999) is higher than the national average (44.8%, 2003). The Otokuni District was designated as a prostate cancer screening area, primarily because PSA examination was successfully incorporated in basic health screening, and because the system of referral from other hospitals and general practitioners to the core hospital (clinic-hospital cooperation) has been matured to a functional level.

Concerning reports on prostate cancer screening in Japan sponsored basically by local administrative organizations, Kuwahara *et al.* reported that 2212 were screened in Natori, Miyagi Prefecture during a 7-year period,[10] and Terai *et al.* reported that 1995 were screened in Okayama Prefecture during an 8-year period.[11] In the Otokuni District, the number of residents who attended primary screening increased, because about 80% of the screenees were screened individually as a result of the incorporation of the PSA test in basic health screening. Recently, PSA has also been examined as a part of basic health screening in other areas of Japan.[12]

In promoting screening for prostate cancer in a particular area, the percentage of the population in the area previously exposed to the PSA test (exposure rate) must be estimated to set the target age level of the screening. We tried to calculate the exposure rate of PSA screening using two methods. Despite the difference between the above two values, the exposure rate in the Otokuni District is considered to be high as a value of annual screening in local municipalities compared with 5.3% in the Gunma Prefecture,[8] and comparable to the value in the United States.[13]

To improve the detection rate of prostate cancer, the efficient selection of screenees for secondary screening including prostate needle biopsy is necessary. In the Otokuni District, people aged 55 years and over are screened. In Japan, the cancer detection rate in the population aged 50–54 years is 0.10%, which is lower than 0.25–2.55% in other age levels, but the evaluation of whether the screening age should be lowered to 50 years may become necessary in the future in consideration of the importance of early detection in younger patients.[14]

For the efficient selection of screenees for prostate needle biopsy, the use of the age-specific PSA reference,[9] PSA velocity,[15] and free/total PSA ratio[16] as well as PSAD, which we are using, has been reported. Our evaluation was negative regarding the usefulness of the age-specific PSA reference for prostate cancer.[17] However, Ito *et al.* reported that the age-specific PSA reference range cut-off value in this setting demonstrated a better diagnostic efficiency than the standard cut-off value of PSA and the age-specific PSA reference range determined by the 95% confidence interval.[9] Annual calculation of the PSA velocity in screenees with an initial PSA level of 1.0–4.0 ng/mL has been reported to have improved the diagnostic accuracy of prostate cancer.[15]

While various factors have been proposed by different institutions for the proper selection of candidates for prostate biopsy, no conclusion has been reached as to which is the optimal parameter for the evaluation of the indication for the procedure. On the basis of the evidence shown by the Watanabe Team,[5] we have evaluated the indication for biopsy according to the PSAD for 10 years. There has been no report on the use of the PSAD for mass screening, but, of the screenees undergoing secondary screening for the first time, prostate cancer was detected in 24% (118/487) and 52% (65/124) with PSA levels of 4.1–10.0 ng/mL and 10.1 ng/mL or higher, respectively. The cancer detection rate based on the PSA range was comparable to the average detection rate in Japan.

Of the 1436 screenees in whom the PAS level was 4.1 ng/mL or higher, biopsy was indicated in 944 (66%), and it could be circumvented in 492 (34%). Of the screenees who underwent secondary screening for the first time and were exempted from biopsy, because their PSA level was below the cut-off value, only 16% (23/147) were later diagnosed to have prostate cancer, and a considerable part of the screenees were repeatedly screened. An appropriate number of screenees should be selected for biopsy in consideration of the ability of the pathologists handling biopsies in the area, but this should not allow cancer to be overlooked. While the PSAD is useful for avoiding unnecessary biopsies, the fact that 45.3% (122/269) of the screenees did not undergo secondary screening thereafter suggests that the education of PSA-positive individuals to serially attend prostate cancer screening is necessary to maintain the reliability of the screening system.

Ito *et al.*[18] detected prostate cancer in 440 screenees by prostate cancer screening in the Gunma Prefecture between 1992 and 2001, and reported that the median age of patients was 69–71 years and that the percentage of patients with T1c/T2N0M0 disease was 56.3–76.9% during those 10 years. The age of patients and the clinical stage of the disease were very close to our results. The European Randomized Study of Screening for Prostate Cancer (ERSPC) also reported that the stage of the disease in 84.4% of the cancers detected in 1269 patients by screening was T1c/T2N0M0, and prostate cancer was detected in an early stage by screening.[19] In both the Otokuni District and the Gunma Prefecture,[18] where screening has been performed annually, prostate cancer tends to be detected at a progressively earlier stage. The American Urological Association sets a life expectancy of 10 years or longer as a criterion for the screenee selection for prostate cancer, and, of the randomized controlled trials reported in the past, the Quebec Study[20] set 80 years, and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening[21] set 74 years as the upper limit of screenees' age. Therefore, comparison of the age of patients at the time of detection of prostate cancer between our and the above studies is impossible.

Since the mean age of prostate cancer patients registered in Japan was 71.8 years at diagnosis,[22] no young age migration was suggested in the prostate cancer patients detected by screening in Gunma or Otokuni. For the future, comparison of the prostate cancer mortality rate between the whole of Japan and the Otokuni District is indispensable to examine whether the high PSA exposure and early detection rates by this screening system are causing lead time bias.

Conclusion

The results of prostate cancer screening in which the PSAD is used for secondary screening are presented. In Japan, the use of the basic health screening system leads to a wider recognition of primary prostate cancer screening and increases in the screening rate. In the Otokuni District, the PSA exposure rate was extremely high (65% with the application for the rate of screenees whose PSA level was 4.1 ng/mL or above), and whether this leads to a decrease in prostate cancer mortality must be evaluated. Comparative analysis of the PSAD with the age-specific PSA reference, free/total PSA ratio, and PSA velocity with regard to the appropriate setting of the interval and quality control of primary screening and detailed evaluation of the frequency of insignificant cancers using total prostatectomy specimens are necessary.

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Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

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Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

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Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ