and 40% depending on the extent of local resection and method of pathological evaluation, which in turn means more than half of the patients do not need radiation therapy. Therefore, some trials have been conducted to specify subgroups that do not require radiotherapy. In hormone receptor positive patients over 70 years of age, radiotherapy may be omitted with proper use of hormonal therapy because of relatively small benefit [14]. However, no other subgroup in which radiotherapy can be omitted has been specified [15]. In various treatment guidelines, it is recommended that WBRT should be performed in all patients after BCS.

According to a survey in Japan, radiotherapy is performed in approximately 70% of patients following BCS [16]. In the United States, the percentage is approximately 80% [17]; a relatively large number of patients do not undergo radiotherapy. This is possibly because radiotherapy requires a considerable expenditure and many hours.

The importance of systemic adjuvant therapy in breast cancer treatment has been increasing. Even in patients with early breast cancer for whom BCT is indicated, several months of chemotherapy is increasingly being given early after surgery, raising the issue of the order of chemotherapy and radiotherapy.

Thus, accelerated partial breast irradiation (APBI), in which the tumor bed is topically irradiated over a short period after BCS, was proposed.

Rationale of APBI

APBI was established based on the following rational background:

1. In more than 70% of patients with IBTR after breast-preserving therapy, recurrence is detected at the periphery of the primary tumor (true recurrence/marginal miss [TR/MM]) [18, 19]. The incidence of recurrence elsewhere (elsewhere failure [EF]) is similar to that of contralateral breast cancer; a "second cancer" may develop following treatment.
2. The treated volume is smaller than that of WBRT. Therefore, hypofractionated irradiation, in which the number of fractions is decreased by elevating the dose per fraction, may not cause significant late toxicities.
3. The radiation dose to the normal breast tissue other than the tumor bed is minimized, facilitating additional conservative therapy including radiotherapy, even when IBTR occurs in the future.
4. APBI can be completed within 1 week after surgery. Therefore, radiotherapy can be initially performed even in patients requiring chemotherapy; delayed radiotherapy dose not influence local control.

Indication for APBI

APBI is not indicated for all patients in whom BCT is selected. Previous studies have indicated that the IBTR rate after APBI was high in high-risk patients including those with large tumors, marked intraductal spreading or the presence of an extensive intraductal component (EIC), and young patients. Furthermore, this procedure has some limitations with respect to irradiation techniques; for external beam irradiation, the normal breast tissue including overlying skin, contralateral breast, heart, and lungs other than the tumor bed are exposed to an excessive dose of radiation. For brachytherapy, an excessive dose of radiation to overlying skin may be problematic.

Methods of APBI

APBI methods are mainly classified into three categories: brachytherapy, intraoperative radiation therapy (IORT), and external beam radiation therapy (EBRT). The following five techniques have been reported.

Brachytherapy

Topical irradiation is performed by placing a radioactive source in the tumor bed. Irradiation can be performed immediately after insertion, and takes 4 days to 1 week. The reproducibility of irradiation is favorable. However, the radiation dose in normal tissue, especially the overlying skin, is problematic. When inserting an applicator during surgery, irradiation can be started immediately following surgery. However, it is impossible to examine pathological margin status. Based on the type of applicator, brachytherapy is classified into two subcategories: multicatheter interstitial brachytherapy and intracavitary brachytherapy.

Multicatheter interstitial brachytherapy [20–25]

In the tumor bed, several guide tubes are placed in parallel at an equivalent interval on a single or several planes. Via these guide tubes, irradiation is performed using remote afterloading of ^{192}Ir. Initially, some studies employed a low dose rate (LDR) system [21]. However, recent studies have mainly selected a high dose rate (HDR) system [20, 23, 24]. Prescribed doses are approximately 50 Gy/5 days for LDR and 30–40 Gy/5 days (twice a day) for HDR. Guide tubes can be inserted during or after surgery. When inserting them during surgery, the lumpectomy cavity may be sutured. However, when inserting them following surgery, a removal cavity should be maintained to specify the tumor

bed from the outside. At the end of irradiation, guide tubes are percutaneously removed.

Intracavitary brachytherapy [26, 27]

Following surgery, a balloon-type applicator (Mammosite®) is inserted into a lumpectomy cavity under ultrasound-guidance. For irradiation, a radioactive source (^{192}Ir) is placed at the center of the balloon using the remote afterloading method. The removal cavity cannot be sutured. After balloon insertion/inflation, the distance from the skin cannot be maintained in some cases, or a space between the balloon and the removal cavity may affect dose distribution, making irradiation impossible; therefore, patients should be informed about such conditions prior to the procedure.

IORT [28, 29]

For IORT, the removal cavity is irradiated in the same room immediately after lumpectomy. Electron beam or low-energy X-ray is used. There are no limitations regarding the reproducibility of treatment or excessive radiation of the skin. However, it is impossible to examine pathological findings including the resection margin status prior to irradiation. In Japan, radiation shielding is another issue. Concerning electron beam application, the use of a self-shielding type device (Mobetron®) may minimize any necessary remodeling of an operating room. As a soft X-ray generator has low energy, it is not necessary to perform operating room remodeling.

IORT using electron beam [29]

Using a specially designed instrument for wound opening, an electron beam applicator is applied to the tumor bed, and anterior one-field electron beam irradiation is performed. Veronesi et al. performed single-dose irradiation at 21 Gy based on the results of a dose escalation study. Unnecessary radiation to underlying normal tissue can be avoided by mobilizing the mammary gland during surgery and placing a lead plate for shielding on its dorsal surface. As single-dose irradiation is completed during surgery, a removal cavity can be sutured.

IORT using soft X-ray [28]

Using a special soft X-ray generator with a bulbous applicator, the applicator is inserted into a removal cavity for irradiation before the cavity is sutured after lumpectomy. The dose gradient is steep. Vaidya et al. performed single-dose irradiation at 20 Gy in an area 2 mm distant from the stump and at 5 Gy in an area 1-cm distant from the stump. The device is smaller than an electron beam device (linear accelerator), and easy to manage.

EBRT (3D-conformal radiation therapy) [30–32]

Using the three-dimensional conformal technique, external beam irradiation is performed on the tumor bed. Radiotherapy treatment planning is performed based on CT images. However, to specify the target volume, the removal cavity should not be sutured, or when it is sutured, it must be marked with metal clips. There is enough time to review pathological findings. Various beam arrangements have been proposed [33, 34]. However, there are limitations such as the reproducibility of each fraction of irradiation and the radiation exposure of normal organs in the beam path. Recent studies with proton beams showed that the dose distribution was better than that for photon 3D-CRT or photon/electron 3-port irradiation [32, 35].

The features, merits, and limitations of each procedure are summarized in Table 1. There are differences in the timing of the pathological evaluation of the resected stump, work required for the procedure, and the reproducibility of treatment.

Table 1 Characteristics of modalities used in APBI

	Pathological confirmation before APBI	Work/ resource required for APBI	Conformity of APBI	Reproducibility of APBI
Interstitial (multicatheter)	Δ	Δ	Δ ~ ○	○
Intracavitary irradiation	Δ	○	Δ ~ ○	○
IORT (electron beam)	×	Δ ~ ×	○	○
IORT (soft X-ray)	×	Δ ~ ×	Δ ~ ○	○
3D-CRT	○	×	×	Δ

○ No problem; Δ some problem; × problematic

For IORT, it is impossible to accurately evaluate tumor pathology, especially the state of the resection margin, before irradiation. However, unnecessary irradiation in areas other than the target volume can be reduced. EBRT can be performed after obtaining pathological information. However, the inter-fractional reproducibility is lower than that of brachytherapy and IORT.

Results of APBI

The results of APBI previously reported are shown in Table 2. In some studies, local control was good, but not in others. In studies in which patients with large tumors, young patients, and those with an extensive intraductal component were regarded as eligible, the risk of local recurrence was high, suggesting the importance of patient selection in successful APBI.

Criticism of APBI

The rapid widespread use of APBI in clinical practice in the United States has contributed to advances in BCT. However, not all radiation oncologists agree with this strategy [36, 37]. The first goal of APBI is tumor control in the breast on the affected side. However, a consensus regarding the long-term results in comparison with WBRT has not been reached, although some studies have indicated that the short-term results obtained were similar to those of WBRT. APBI is effective at a 2 cm distance from the resected stump. Some researchers are skeptical about the difference between wider resection and APBI. In a randomized controlled trial of BCS, with or without WBRT, in which wider resection (quadrantectomy) was used as protocol treatment, the addition of WBRT still decreased the ipsilateral breast recurrence rate [38]. This suggests that WBRT is more advantageous than APBI.

In APBI, cancer recurrence in areas other than the periphery of the primary tumor bed is not considered. However, it is controversial whether such recurrence, which has been reported in a specific number of patients, may be ignored.

In addition, recent studies reported that WBRT improved the survival rate in patients undergoing BCT [39, 40]. The theoretical background of this benefit remains to be clarified. However, some investigators suggested that WBRT improves survival in a similar fashion to post-mastectomy radiation therapy (PMRT); it improves tumor control not only in breast tissue but also in lower axilla, skin, and subcutaneous tissue in the radiation field, which prevents subsequent secondary dissemination [40]. It should be investigated whether APBI achieves ipsilateral breast control as well as all the benefits of WBRT in a large number of patients over a prolonged period.

NSABP B-39/RTOG 0413 trial

In 2005, a phase III NSABP B-39/RTOG 0413 collaborative comparative study was started to compare WBRT with APBI. According to an RTOG announcement, more than 150 patients per month were registered (as of May 2006). More than 70% of them underwent APBI by external irradiation. Initially a study of 3,000 patients was planned, but this was increased to 4,300. The eligibility criteria were disadvantageous for APBI in that young patients (18 years or older), those with T2 tumors (3 cm or less), those with EIC/DCIS, and those with lymph node metastasis (three or less positive nodes) were eligible, in whom the results of previous studies have suggested an increase in the local recurrence rate. If this clinical study shows that APBI is as effective as WBRT, APBI may become the main irradiation procedure after BCS.

Limitations of APBI in Japanese patients

The most important issues are breast size-related differences in the technique and the relationship between the removal cavity and the skin.

In Europe and the United States, a cavity after extirpation of the main tumor is maintained in many patients. However, in Japan, the cavity is sutured for cosmetic reasons. In this case, it is impossible to insert a device for intracavitary irradiation. For external irradiation, the target of irradiation can be visually confirmed when the margin of the removal cavity is marked with metal clips. However, the entire resected stump cannot always be accurately identified.

In Europe and America, the breast size is generally large, and lumpectomy, in which the extent of resection is about 1 cm from the gross tumor, is frequently performed. Therefore, the mammary gland tissue remains on the lateral, dermal, and pectoralis muscle sides of the removal cavity. In such cases, all-direction irradiation using a Mammosite® device is useful.

In Japan, the breasts are generally smaller, and wide excision involving a 2-cm free margin from the tumor is most commonly performed. In many cases, mammary gland tissue does not remain on the dermal or pectoralis muscle sides of the tumor. The target of irradiation is only the lateral stump. However, the dose distribution in the dorsoventral direction cannot be controlled with a Mammosite® device; therefore, an excessive dose of irradiation to the skin may be a treatment-limiting factor.

Recently, a new device (SAVI™, BioLucent, Inc., California, USA), in which multi-channel guide tubes at

Table 2 Results of APBI in Western countries

Series	*N*	Age	Size	Surgery	Margin status	EIC/DCIS allowed	Axillary LN
Guy's Hospital [21]	27	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Dissection in all pts.
Guy's Hospital [20]	50	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Level 3 dissection performed
NCI Budapest [24]	45	NR 38–78	<2 cm	Wide excision	Negative microscopically	Not allowed	Single nodal involvement allowed
WBH [25]	199	>40	<3 cm	Lumpectomy	≥2 mm 2 pts. 0–2 mm	Not allowed 21 pts. in-situ	12% 1–3 positive node
London Regional [23]	39	NR 39–84	<5 cm	Lumpectomy	Negative	Eligible	15% positive
Osaka Medical Center [22]	20	>20 32–72	<3 cm	Wide excision	1.5–2 cm macroscopically	Eligible	Level 1–2 dissection performed
					3/20 positive in final pathology		Positive in 3/20
WBH [26]	80	>40	≤3 cm	Local resection	≥2 mm	Eligible	≤3 positive nodes
NCI Milan [29]	101	NR 33–80	≤2.5 cm	Quadrantectomy	>1 cm macroscopically	No data	SNB or dissection in 96/101
Christie Hospital [30]	353	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Clinically negative No dissection
NYU [31]	40	Post menopausal	<2 cm non-palpable	Lumpectomy	≥5 mm	Not allowed	No data
MGH [32]	20	NR 46–75	≤2 cm	Lumpectomy	≥2 mm	Not allowed	Pathologically negative

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Guy's Hospital	LDR ^{192}Ir multicatheter	55 Gy/5–6 days	6 years	37% crude	70% actuarial read from figure	No data	83%
Guy's Hospital	MDR ^{137}Caesium	45 Gy/4 fr./4 days	6.3 years	18% crude	No data	No data	81%
NCI Budapest	HDR ^{192}Ir multicatheter	30.3–36.4 Gy/7 fr./4 days	81 mo. median	6.7% crude	93.3% actuarial cancer specific survival	Grade 3 fibrosis 2.2% Symptomatic fat necrosis 2.2%	84.4%
WBH	120 pts.: LDR 79 pts.: HDR	LDR: 50 Gy/4 days HDR: 32 Gy/ 8 fr./ or 34 Gy/10 fr.	65 mo. median	1% actuarial	87% actuarial OS	0%	99%
London Regional	HDR ^{192}Ir multicatheter	HDR: 37.2 Gy/ 10 fr./5–7 days	91 mo. median	16.2% actuarial at 5 years	86% actuarial OS	No data	Median subjective score 90/100
Osaka Medical Center	HDR ^{192}Ir multicatheter	HDR: 36–42 Gy/6–7fr./3–4 days	52 mo. median	5% crude	89% actuarial OS	Grade 3:5%	75%
WBH	Intracavitary (Mammosite)	34 Gy/10 fr./5 days	22.1 mo. median	2.9% 3 year actuarial	91.3% 3 year OS	No data	88% 3 year
NCI Milan	IORT (electron)	10–21 Gy Single dose 10–15 Gy with EBRT	42 mo. median	2% crude	98% crude	Grade1–2 22% Grade 3:1%	No data

Table 2 continued

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Christie Hospital	EBRT (electron)	40–42.5 Gy/8 fr./10 days	8 years	25% actuarial	73% actuarial[a]	Marked telangiectasis 33% Marked fibrosis 14%	No data
NYU	EBRT (photon)	30 Gy/5 fr./10 days	12 mo.	0%	0%	No data	No data
MGH	EBRT (proton)	32 CGE/8 fr./4 days	12 mo.	0%	100%	Telangiectasia 3pts. Rib fracture 1 pt	100%

WBH William Beaumont hospital, *MGH* Massachusetts general hospital, *NYU* New York University, *NR* not restricted, *SNB* sentinel node biopsy, *LDR* low dose rate, *HDR* high dose rate, *CGE* cobalt gray equivalent, *F/U* follow-up, *OS* overall survival

[a] Read from survival curve

the circumferential region facilitate the fine control of dose distribution on the inner wall of the resected cavity, was developed. However, treatment results have not been published yet.

External irradiation also has a similar limitation. When irradiation is performed in the supine position, flat extension of the breast reduces the distance between the target of irradiation and the skin, leading to excessive radiation exposure of the skin.

For external irradiation, the conformity of dose distribution is less favorable than that for other procedures. As reported by Kosaka et al., the radiation dose administered to the normal mammary gland may be excessive when the resected cavity is relatively large compared with the breast.

When the breast size is large to some degree, these limitations may be overcome by suspending the breast in the prone position for irradiation. However, no study has investigated this issue in Japanese women.

Conclusion

Currently, we cannot recommend APBI as a standard option for BCT. However, in Europe and the United States, this procedure is being increasingly employed in clinical practice. If the results of clinical studies are good, it may accelerate this tendency. BCT in Japan markedly differs from that in Europe and the United States with respect to the surgical procedures and the average body habitus. In introducing APBI, unique strategies must be established and inspected.

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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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New trends in radiation therapy as a component of breast conserving therapy

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Keywords Breast conserving therapy · Radiation therapy · Accelerated partial breast irradiation · Shorter course whole breast radiation therapy

The importance of radiation therapy as a component of breast conserving therapy (BCT) is well established in Japan: according to a national survey by the Japanese Breast Cancer Society, more than 70% of patients undergoing BCT receive radiation therapy.

Whole breast radiation therapy (WBRT) of 45–50 Gy given in 1.8–2.0 Gy daily fractions with or without boost irradiation to the tumor bed has been the standard of care for many years.

Recently, new concepts of radiation therapy such as shorter course WBRT and accelerated partial breast irradiation (APBI) have been attracting wide attention from the breast cancer community. Shorter course WBRT comprises 40–44 Gy given in 15–16 fractions. It is used in Canada and parts of Europe where facilities for radiation therapy are sparse. A randomized controlled trial in Canada proved the equivalence of shorter course WBRT both in tumor control and cosmetic outcome. This may be particularly useful in Japan where rapidly growing demand for radiation therapy is placing pressure on limited resources for radiation therapy. This approach is also beneficial to patients because of the reduced cost of radiation therapy.

In APBI, only the removal cavity is the target of radiation therapy. This means that an even larger fraction size can be used, and the radiation therapy is completed within 1 week. Various approaches have been proposed for APBI, including multi-catheter interstitial brachytherapy, intracavitary brachytherapy, external beam radiation therapy, and intra-operative radiation therapy. Although the results of randomized controlled trials in terms of testing the equivalence of APBI and WBRT are still awaited, the number of patients in the United States who choose APBI over WBRT is rapidly growing.

Both of these new approaches may eventually become standard options in Japan if the subjects are appropriately selected; however, one important issue must be addressed before these new techniques are used in daily practice. Because both techniques use a larger fraction size than conventional WBRT, the possibility exists of enhanced late radiation damage to normal tissue. As there are obvious differences in physique between women in Japan and those in Western countries, and as radiation dose distribution largely depends on the size and shape of the breast, caution is necessary when interpreting results from Western countries: the safety of such treatment should first be tested in Japanese patients. In this special feature, these new techniques are reviewed from the viewpoint of Japanese radiation oncologists. Initial clinical results of shorter course WBRT and experimental results of the feasibility of APBI using 3D conformal radiation therapy in Japanese women are also reported.

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Patterns of Pretreatment Diagnostic Assessment and Staging for Patients with Cervical Cancer (1999–2001): Patterns of Care Study in Japan*

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Objective: To evaluate the patterns of pretreatment diagnostic assessment in uterine cervical cancer patients treated with definitive radiotherapy in Japan.
Methods: The Japanese Patterns of Care Study working group conducted a second extramural audit survey of 68 institutions and collected specific information on 631 patients with cervical cancer. All patients were treated with radiotherapy in 1999–2001. Of these, 324 patients treated without surgery were the subjects of this study.
Results: International Federation of Gynecology and Obstetrics-prescribed diagnostic procedures were performed at moderate rates in our study cohort. The performance rates of chest X-ray, intravenous urography, cystoscopy, and proctoscopy were 74, 54, 53, and 33%, respectively. Cross sectional imaging studies were frequently performed. Pelvic CT, abdominal CT, and pelvic MRI were performed in 88, 80, and 76%, respectively. Lymphangiography (1%) and surgical evaluation (1%) were rarely done. Only one patient underwent PET scans in this survey period.
Conclusions: This study demonstrated the patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy in Japan.

Key words: cervix neoplasm – radiotherapy – patterns of care – FIGO

INTRODUCTION

The pretreatment assessment of cancer extension is extremely important for prognosis estimation and treatment planning. Additionally, a well-defined initial assessment enables the comparison of cancer treatment results among institutions or different treatment methods. The International Federation of Gynecology and Obstetrics (FIGO) provides a global staging system for gynecologic cancers (1). Most clinicians use this staging system in the treatment of uterine cervical cancer. The system describes the rules for stage classification in detail, and the permitted diagnostic procedures are clearly stated. However, some of the procedures included, such as intravenous urography, and skeletal X-rays, could be considered outdated. Although tumor diameter and pelvic nodal status are not accounted for in the FIGO staging system, they are estimated to be the important prognostic factors for cervical cancer (2). In several studies, tumor diameter as assessed by MRI was a significant prognostic indicator for patients with cervical cancer (3–5). Evaluation of pelvic or para-aortic lymph node status with optional imaging studies, such as CT, MRI, and lymphangiograpy, may also be useful for predicting prognosis (6).

Several studies describe the patterns of pretreatment work-up of cervical cancer in the USA (7–9); however, there are few studies from Japan. The objective of this study

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was to review the patterns of pretreatment diagnostic assessment of cervical cancer in Japan.

MATERIALS AND METHODS

Between July 2002 and June 2004, the Japanese Patterns of Care Study group (JPCS) conducted a national survey of patients with cervical cancer treated with radiotherapy. Sixty-eight out of 640 institutions were selected for the survey with a stratified 2-staged cluster sampling method (10). Prior to random sampling, all institutions were classified into one of four groups. The criteria for stratification have been detailed elsewhere (10). In brief, the JPCS stratified Japanese institutions as follows: A1, academic institutions treating $\geq$430 patients annually; A2, <430 patients; B1, non-academic institutions treating $\geq$130 patients annually; B2, <130 patients. Academic institutions included cancer center hospitals and university hospitals. Non-academic institutions consisted of other facilities, such as national, prefectural, municipal, and private hospitals.

The JPCS surveyors performed on-site chart reviews at each participating facility using an originally developed format for cervical cancer. Data collection included patient characteristics (e.g. patient history, age, performance status, laboratory data, pathology, and stage), details of pretreatment work-up, therapeutic information (e.g. radiotherapy, chemotherapy, and surgery), and treatment outcome. Patient eligibility criteria of the survey were as follows: (i) carcinoma, (ii) treatment between January 1999 and December 2001, (iii) no distant metastases, (iv) no prior or concurrent malignancy, (v) no gross para-aortic lymph node metastases, and (vi) no previous pelvic radiotherapy. 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 (definitive radiotherapy) were analysed. 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. Cases with 'unknown' and 'missing' values were combined in the tables because their meanings were the same in most cases: no valid data were found in the given resources (11).

RESULTS

Table 1 describes the patient characteristics in the JPCS 1999–2001 survey of cervical cancer patients treated with definitive radiotherapy. Table 2 shows the performance rates of the diagnostic procedures. Of the diagnostic procedures prescribed by FIGO, three quarters of the patients underwent a chest X-ray. Other examinations, such as intravenous urography, cystoscopy, and proctoscopy, were performed in approximately 30–50% of the patients. Table 3 shows the performance of the examinations according to stage. A substantial number of early stage (I, II) patients underwent these diagnostic tests prescribed by the FIGO system. Majority of the patients underwent both pelvic and abdominal CT. Pelvic MRI was also frequently performed. CT and MRI were performed mostly irrespective of stage. Lymphangiography (LAG) and surgical staging were rarely performed. Only one patient underwent PET examination in the survey period.

Tumor diameter was recorded in 75% (242/324). The tumor diameter evaluation rates by FIGO stage were 67% (29/43) for stage I, 83% (85/102) for stage II, 77% (94/122) for stage III, and 80% (28/35) for stage IVA ($P = 0.01$). MRI was the most common modality for evaluating tumor size (47%) followed by CT (16%). Only a small percentage of patients had a tumor size evaluation consisting of only a pelvic examination (6%). Tumor size increased significantly with increasing stage. Median tumor size was 26 mm (range: 0–45 mm) for stage I, 40 mm (range: 15–90 mm) for stage II, 46 mm (range: 15–100 mm) for stage III, and 55 mm (range: 30–100 mm) for stage IVA ($P < 0.0001$). Pelvic nodal status was recorded in 82% (266/324) of the patients surveyed. The pelvic nodal assessment rate by stage was 88% (38/43) for stage I, 86% (88/102) for stage II, 83%

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

Characteristics	No. of patients	(%)
Total no.	324	
Age (years)		
Range	26–100	
Median	71	
KPS		
≤ 70	64	20
80	103	32
90	114	35
100	21	6
Unknown/missing	22	7
Histology		
Squamou 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

KPS, Karnofsky performance status; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Pretreatment diagnostic procedures performed

Procedure	No. of patients	(%)
Chest X-ray		
Yes	241	74
No	7	2
Unknown/missing	76	24
Intravenous urography		
Yes	176	54
No	68	21
Unknown/missing	80	25
Cystoscopy		
Yes	171	53
No	60	19
Unknown/missing	93	28
Proctoscopy		
Yes	108	33
No	114	35
Unknown/missing	102	32
Pelvic CT		
Yes	286	88
No	8	3
Unknown/missing	30	9
Abdominal CT		
Yes	258	80
No	14	4
Unknown/missing	52	16
Pelvic MRI		
Yes	246	76
No	39	12
Unknown/missing	39	12
Lymphangiography		
Yes	3	1
No	241	74
Unknown/missing	80	25
PET		
Yes	1	-
No	254	79
Unknown/missing	69	21
Surgical staging		
Yes	3	1
No	257	79
Unknown/missing	64	20

PET, positron emission tomography.

(101/122) for stage III, and 94% (33/35) for stage IVA ($P = 0.12$). CT was most frequently used for the assessment of nodal status (72%). PET and surgical examination were never utilized for this purpose. Positive nodal status significantly correlated with FIGO stage: 2% for stage I, 6% for stage II, 16% for stage III, and 49% for stage IVA ($P = 0.0001$).

DISCUSSION

This study demonstrated the patterns of pretreatment diagnostic assessment for cervical cancer patients who underwent definitive radiation therapy between 1999 and 2001 in Japan. Several of the cases reviewed in this survey had unknown or missing data; and this was a theoretical weaknesses of our audit. Inclusion of cases with incomplete information in the ratio calculations, however, reduced the potential for overestimation of performance rates of the tests.

FIGO permitted procedures were performed more frequently than expected in the patients surveyed. The use of FIGO permitted examinations (e.g. intravenous urography, cystoscopy, and proctoscopy) is gradually decreasing in the USA (7–9). In a 2000–02 US study on the pretreatment evaluation of patients with stage IIB or less disease, the rates for performing intravenous urography, cystoscopy, and proctoscopy were 1, 16, and 17%, respectively (9). In contrast, the present study demonstrated that these exams were performed frequently even for early stage cases in Japan. Schmitz et al. (12) proposed that since the likelihood of upstaging using these examinations was very low in clinical stage IB patients, these exams could be omitted in those with stage IB disease. Now, the National Comprehensive Cancer Network (NCCN) guideline states that cystoscopy and proctoscopy are optional exams for the pretreatment assessment of cervical cancer patients with a disease stage of IB2 or higher (http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf).

This study demonstrated that CT and MRI were routinely utilized during the surveyed period in Japan. Tumor size and pelvic nodal status are considered to be extremely important prognostic factors for cervical cancer (2). Several studies showed the accuracy of MRI for measuring tumor diameter for uterine cervical cancer (13,14). In the 1990s, several researchers reported that tumor diameter, as assessed by MRI, significantly affected the outcome of cervical cancer patients treated with definitive radiotherapy (3–5). The radiological evaluation of lymph node metastases is also valuable in cervical cancer patients, with both CT and MRI having high predictive values (6). MR imaging had an accuracy of 93%, with 62.2% sensitivity and 97.9% specificity when a minimum axial diameter of 1.0 cm was adopted as a size criterion for detection of pelvic nodal metastases (15). The results of our study reflect the penetration of these findings into the clinical practice in Japan. Unfortunately, we were unable to precisely measure the performance rates of the assessments of tumor diameter and lymph node status due to a flaw in the survey format. Namely, we were unable to distinguish whether the assessments were performed by

Table 3. Pretreatment diagnostic procedures performed according to the FIGO stage

Procedure	Stage				Missing/unknown
	I	II	III	IVA	
Intravenous urography	17/43 (40%)	53/102 (52%)	74/122 (61%)	26/35 (70%)	6/22
Cystoscopy	18/43 (42%)	58/102 (57%)	64/122 (52%)	25/35 (71%)	6/22
Proctoscopy	12/43 (28%)	32/102 (31%)	43/122 (35%)	17/35 (49%)	4/22
Pelvic CT	40/43 (93%)	89/102 (87%)	112/122 (92%)	34/35 (97%)	11/22
Abdominal CT	35/43 (81%)	83/102 (81%)	103/122 (84%)	29/35 (83%)	8/22
Pelvic MRI	31/43 (72%)	84/102 (82%)	88/122 (72%)	27/35 (77%)	16/22

the treating physicians or were performed anew by the visiting surveyors at the time of the analysis. Despite this limitation, we were able to roughly approximate the tumor diameter and the lymph node status in each stage. In the next JPCS presently being conducted, the format has been revised to clarify the aforementioned points. Our data will aid in comparing outcome between Japan and other countries. Abdominal CT has diagnostic value in detecting extrapelvic metastases (i.e. liver and para-aortic node) and the presence of hydronephrosis or a non-functioning kidney. Despite the potential usefulness of CT and MRI, these cross-sectional imaging studies are listed as optional examinations in the FIGO system (1). FIGO also acknowledges the usefulness of these exams. However, FIGO does not accept them for staging purposes, primarily because these instruments are not generally available in developing countries. The FIGO system clearly states that findings from these exams should not be the basis for staging (1). Improper application of these exams could lead to staging migration (2). However, we believe that these cross-sectional imaging studies should be applied universally not to determine FIGO stage but to assess important prognostic factors, namely tumor diameter and nodal status.

Several randomized clinical trials (RCTs) performed in the USA demonstrated the therapeutic value of concurrent chemoradiotherapy (http://www.cancer.gov/newscenter/cervicalcancer). Most of these trials required extensive evaluation of para-aortic lymph nodes by surgical exploration or LAG. This limits the translatability of the recommendations from these trials to the Japanese clinical practice. LAG and surgical staging were rarely performed for patients in our survey. Although Eifel reported that lymph nodal status was assessed by LAG in 13.6%, and surgical evaluation in 12.2% in the US PCS (1996–99), other studies revealed that, the performance of LAG has been decreasing recently (7–9). A similar problem exists in the evaluation of tumor diameter. In the US RCTs, tumor diameter was determined by physical examination. However, tumor size assessment by physical examination is highly subjective. Thus an objective method such as CT or MRI is preferable particularly when patients are being stratified in a clinical trial. This would facilitate the translation of evidence to clinical practice.

PET was rarely performed during the study period in Japan despite being shown to be useful in the late 1990s (16). Its application is expected to increase in the future, because the Japanese health insurance plan has covered it since 2004.

In summary, the JPCS describes the general patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy during 1999–2001 in Japan. Patterns of pretreatment work-up should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

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Conflict of interest statement

None declared.

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Impact of radiation therapy on breast-conserving therapy for breast cancer in Japanese women: A retrospective analyses of multi-institutional experience. Kansai Breast Cancer Radiation Therapy Study Group

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Abstract. Whole breast radiation therapy (RT) after breast-conserving surgery is sometimes omitted in Japan; however, its impact on the outcome has not been properly evaluated. A multi-institutional retrospective study was conducted to clarify the impact of RT on local control after breast-conserving therapy (BCT). Data were collected from 3576 patients from 37 participating hospitals, of whom 1763 were eligible for analyses. Five hundred and five patients had ipsilateral breast tumor recurrence (IBTR) and 1258 patients did not. Details of IBTR were available for 245 of 505 patients who had IBTR, the location of IBTR was within or adjacent to the original tumor bed in 168 patients (68.6%). IBTR was salvaged with partial mastectomy in 119 patients (48.6%). Second recurrence in the ipsilateral breast was observed in 27 patients (11.0%). Univariate analyses demonstrated that administration of RT, the resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR. Multivariate analysis demonstrated that administration of RT, T stage and N stage were significantly correlated to IBTR. Among them, administration of RT had the largest impact on RT and it decreased the risk of IBTR by 77.3%. Omission of RT had the most significant impact on IBTR. RT should be given as a standard component of BCT.

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Key words: breast cancer, breast-conserving therapy, radiation therapy, ipsilateral breast recurrence

Introduction

The incidence of breast cancer in Japanese women has become the highest among various cancers and it was estimated that 40675 women were newly diagnosed with breast cancer in 2001. The ratio of patients who undergo breast-conserving surgery (BCS) is also increasing and BCS has become the most frequently employed method of initial surgery for breast cancer in Japan (1). According to the NIH consensus statement, breast-conserving therapy (BCT) comprises of BCS and adjuvant radiation therapy (RT). The role of RT in BCT has been well established as a result of at least 8 randomized controlled trials and meta-analyses of these trials (2-10). Moreover, the subgroup of patients who do not receive a benefit from RT after BCS has not been defined in spite of various attempts to find such a subgroup. In Japan, however, ~20% of patients who undergo BCS do not receive RT (1). This number is larger than in the USA (11). One reason for not receiving RT in Japan is that some surgeons believe that RT is not necessary if the tumor was resected with an ample pathologically negative margin and that RT is harmful and deteriorates the cosmetic outcome. To clarify the impact of RT on ipsilateral breast tumor recurrence (IBTR) in such practice in Japan, we collected data from participating institutions of the Kansai Breast Cancer Radiation Therapy Study Group (KBCRTSG) and analyzed them retrospectively.

Patients and methods

Study design. This study was conducted as a multi-institutional retrospective review. The primary endpoint was IBTR, including those preceded by any form of regional and distant recurrence.

Patients. Between August 2004 and February 2005, data from 3576 patients were collected from 37 participating hospitals in