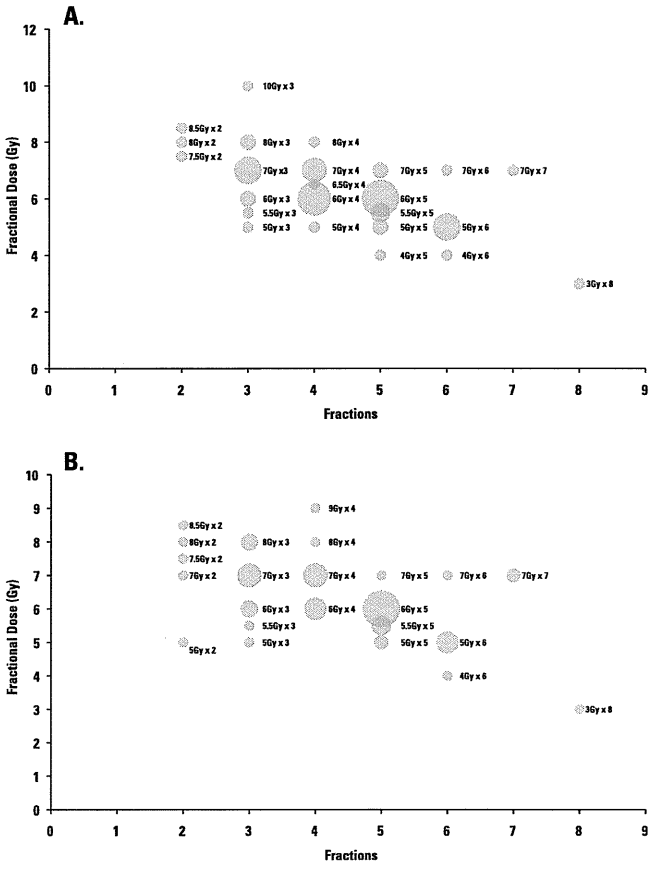

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages IIB–IVA cervical cancer. The size of the circle is proportional to the number of respondents, with the largest number reporting 6 Gy for five fractions.

was 0.51 (SD 0.03), which was significantly different from the average ratio for all other countries (p = 0.0002). When stratified by stage, this difference in brachytherapy ratio was seen only for the Stage IB–IIA subgroup. For Japanese respondents, the ratio of brachytherapy to EB plus brachytherapy was 0.58 (SD 0.05) for Stage IB–IIA and 0.45 (SD 0.06) for Stage IIB–IVA (p = 0.002). In other words, to accommodate their reduced EBRT dose, the Japanese use a higher brachytherapy dose for patients with Stage I–IIA tumors than that typically used elsewhere.

Complications

When queried about the number of patients treated for cervical cancer who were hospitalized annually for a complication, most respondents indicated 0 (n = 12, 17%), 1 (n = 37, 60%), or 2 (n = 9, 13%).

DISCUSSION

The primary goal of this survey was to gauge variation in HDR fractionation for cervical cancer and to determine brachytherapy practice patterns internationally, in order to assist with the development of the brachytherapy portion of international randomized clinical trials. Inasmuch as cervical cancer remains a leading cause of mortality in developing countries, international collaborative randomized trials that can advance treatment approaches on a global level are needed. In particular, before undertaking this study, we questioned whether the heterogeneity of brachytherapy practice might hinder standardization. As part of this survey, other items of interest were queried, including the utilization of three-dimensional (3D) imaging during brachytherapy. Other questions were designed to provide a 3-year update to selected general management information queried on the 2007 survey (16).

With regard to the general management of cervical cancer, this survey showed that the use of concurrent chemoradiation is similar to that reported in the 2007 survey, as are EBRT doses. In terms of brachytherapy, a greater proportion of respondents in this survey reported the use of HDR than in a United States–based survey from 1999 (4). However, the use of HDR in the United States also seem to be increasing, with 85% of ABS members having HDR brachytherapy available in their practices in 2007, indicating a growing acceptance of HDR brachytherapy in the United States that matches international implementation (3). The transition from LDR to HDR has been based on an increased acceptance of the feasibility, safety, and efficacy of HDR when carefully administered, with a concomitant increase in the use of 3D imaging. Three-dimensional imaging allows dose optimization away from the normal tissues in an attempt to spare them the large fractional dose used in HDR brachytherapy.

Overall, a significant proportion of GCIG members have access to 3D imaging for gynecologic brachytherapy. The most frequently used method for brachytherapy imaging is CT. In a recent ABS survey, 70% of respondents used CT after brachytherapy applicator insertion, and 57% used CT imaging in this survey (3). Before the 1990s, plain x-ray film simulation was the standard of care. After the integration of CT into radiation oncology departments, 3D imaging use increased and now represents the standard for external beam. The integration of 3D imaging into brachytherapy has also expanded, albeit later than for EBRT. This study found a significant proportion using the best available 3D imaging modality available at their institution, either CT or MRI, for cervical cancer brachytherapy planning.

In this survey, HDR brachytherapy dose fractionation recommendations varied considerably. The most common fractionation internationally was 6 Gy for five fractions, although this regimen is used by fewer than 20% of reporting institutions. Despite the high degree of individuality in brachytherapy prescribing, the biologic equivalence was remarkably similar for all countries and regions except Japan. All six Japanese respondents follow a regimen of treating to 20 to 30 Gy for early stage disease, then place a midline block, which significantly reduce the cumulative EQD2 cervical dose compared to that used in other countries. Nevertheless, the EQD2 dose to the cervix was equivalent, on average 80 Gy for all regions of the world surveyed. The Japanese cervix dose reduction to approximately 70 Gy, instead of the

Table 1. Routine high-dose-rate brachytherapy fractionation regimens for cervical cancer as used by Gynecologic Cancer Intergroup surveyed physicians

Standard fractionation for Stages IB–IIA cervical cancer				Standard fractionation for Stages IIB–IVA cervical cancer			
% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2	% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2
18% (11)	6	5	40	23% (14)	6	5	40
15% (9)	6	4	32	10% (6)	7	4	40
12% (7)	7	3	29.75	10% (6)	7	3	30
8% (5)	5	6	37.5	8% (5)	6	4	32
8% (5)	7	4	39.7	7% (4)	5.5	5	35.5
5% (3)	5	5	31.25	5% (3)	5	6	37.5
5% (3)	5.5	5	35.52	5% (3)	7	6	59.5
3% (2)	8	3	36	5% (3)	6	3	24
1.6% (1)	3	8	26	5% (3)	8	3	36
1.6% (1)	4	5	23.3	3% (2)	7	7	69.4
1.6% (1)	4	6	28	3% (2)	5	5	31.3
1.6% (1)	5	3	18.75	1.6% (1)	3	8	26
1.6% (1)	5	4	25	1.6% (1)	4	6	28
1.6% (1)	5.5	3	21.3	1.6% (1)	7	5	49.6
1.6% (1)	6	3	24	1.6% (1)	8	4	48
1.6% (1)	6.5	4	35.75	1.6% (1)	9	4	57
1.6% (1)	7	5	49.6	1.6% (1)	5	3	18.8
1.6% (1)	7	6	59.5	1.6% (1)	5.5	3	21.3
1.6% (1)	7	7	69.4	1.6% (1)	5	2	12.5
1.6% (1)	7.5	2	21.9	1.6% (1)	7.5	2	21.9
1.6% (1)	8	2	24	1.6% (1)	8	2	24
1.6% (1)	8	4	48	1.6% (1)	8.5	2	26.2
1.6% (1)	8.5	2	26.2				
1.6% (1)	10	3	50				

Abbreviation: EQD2 = Equivalent dose in 2 Gy fractions.
Results indicate the diversity of responses.
The EQD2 formula was used to convert the high-dose-rate dose and number of fractionations.

international standard of 80 Gy, must be further analyzed, including comparison of recurrence rates and toxicities; an upcoming abstract shows reasonable rates of local control (17). The Japanese regimen, in use for several decades, was implemented upon the observation that Japanese women, potentially because of their small body size, had very high bowel and bladder toxicity rates when treated with higher pelvic EBRT doses (18). The current Japanese regimen begins HDR intracavitary brachytherapy once per week after 20 Gy. Whether a genetic difference in sensitivity to radiation exists is unknown, but one implication of the successful outcomes in Japanese women is that brachytherapy may be the more critical component for treatment to the cervix, particularly for early stage disease with a lower risk of nodal spread.

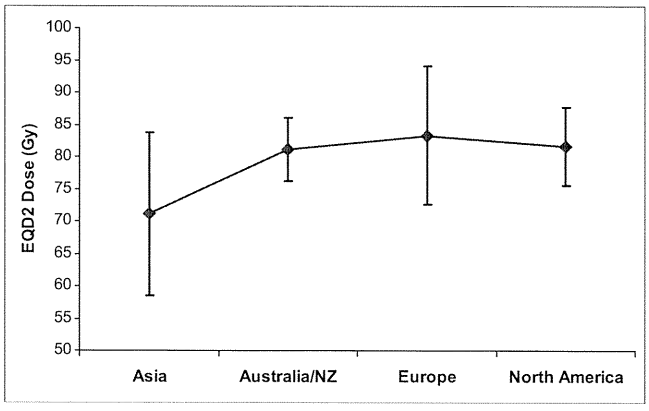

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

A previously unassessed difference in brachytherapy administration was identified with regard to the proportional relationship of brachytherapy to the sum total dose. For early-stage patients, the Japanese respondents administer a significantly higher proportion of the dose using brachytherapy than practitioners from other countries. The reliance on HDR brachytherapy fractionation may indicate that a large dose given with HDR can compensate for a lower external beam dose in patients with small tumors. This assumption of proportionality must be corroborated with recurrence information.

For all respondents (including those from Japan), the mean EBRT plus brachytherapy cumulative EQD2 dose was 80.4 Gy, with a standard deviation of 10 Gy. Patients with higher-stage disease (Stage IIB–IVA) received a significantly higher dose than did those with earlier-stage cervical cancer. Therefore, a dose of 80 Gy may be considered the universally accepted international baseline dose overall, with on average 79 Gy for Stage IB–IIA and 84 Gy for Stage IIB–IVA cases. A dose of 80 Gy is approximately equivalent to 45 Gy delivered with EBRT and 5.5 Gy for five fractions delivered with HDR brachytherapy. A dose

of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for five fractions or 7 Gy for four fractions of HDR.

Standardization of HDR brachytherapy on an international level will assist institutions in terms of comparing toxicities and outcomes in patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR brachytherapy. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes in Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemoradiation may attempt radiation dose variation based on response and on improved sparing of normal tissues with 3D imaging, to determine the acceptable safe threshold level that results in equivalent eradication of disease while minimizing toxicities.

REFERENCES

1. Age-standardized incidence rates of cervical cancer. 2009. (Accessed May 22, 2010, at http://www.who.int/mediacentre/factsheets/fs297/en/).
2. Eifel PJ, Winter K, Morris M, *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. *J Clin Oncol* 2004;22: 872–880.
3. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: A survey of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys* 2010;76:104–109.
4. Erickson B, Eifel P, Moughan J, *et al.* Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): A patterns of care study. *Int J Radiat Oncol Biol Phys* 2005;63: 1083–1092.
5. Stewart AJ, Viswanathan AN. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. *Cancer* 2006;107:908–915.
6. Viswanathan AN, Dimopoulos J, Kirisits C, *et al.* Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: Results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007;68:491–498.
7. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–694.
8. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515–528.
9. Stewart AJ, Bentzen SM. Radiobiological aspects of brachytherapy in the era of 3-dimensional imaging. In: Viswanathan AN, Kirisits C, Erickson B, Poetter R, editors. Gynecologic radiation therapy: Novel approaches to image-guidance and management. Berlin: Springer; 2011.
10. Nag S, Erickson B, Thomadsen B, *et al.* The American Brachytherapy Society recommendations for high dose rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48:201–211.
11. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys* 1999;43:359–366.
12. Forrest J, Ackerman I, Barbera L, *et al.* Treatment outcomes for patients with advanced cervical cancer treated with GOG protocol definitive chemoradiotherapy and HDR brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:S151.
13. Anker CJ, Cachoeira CV, Boucher KM, *et al.* Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; 76:704–712.
14. Haie-Meder C, Potter R, Van Limbergen E, *et al.* Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74: 235–245.
15. Potter R, Dimopoulos J, Kirisits C, *et al.* Recommendations for image-based intracavitary brachytherapy of cervix cancer: the GYN GEC ESTRO Working Group point of view: in regard to Nag, *et al.* (*Int J Radiat Oncol Biol Phys* 2004;60:1160–1172. *Int J Radiat Oncol Biol Phys* 2005;62:293–295. author reply 5–6).
16. Gaffney DK, Du Bois A, Narayan K, *et al.* Practice patterns of radiotherapy in cervical cancer among member groups of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys* 2007;68:485–490.
17. Toita T. Prospective multi-institutional study of definitive radiotherapy and high-dose-rate intracavitary brachytherapy in early stage uterine cervical cancer: A cooperative study of Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG). *Int J Radiat Oncol Biol Phys* 2010;77:S100.
18. Toita T, Kakinohana Y, Ogawa K, *et al.* Combination external beam radiotherapy and high dose rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;56: 1344–1353.

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Clinical Investigation

Patterns of Radiotherapy Practice for Patients with Cervical Cancer in Japan, 2003–2005: Changing Trends in the Pattern of Care Process

Natsuo Tomita, M.D.,* Takafumi Toita, M.D.,† Takeshi Kodaira, M.D.,* Atsunori Shinoda, M.D.,‡ Takashi Uno, M.D.,¶ Hodaka Numasaki, Ph.D.,§ Teruki Teshima, M.D.,§ and Michihide Mitsumori, M.D.**

**Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; †Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan; ‡Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan; ¶Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan; §Department of Medical Physics and Engineering, Graduate School of Medicine, Osaka University, Suita, Japan; and **Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

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Summary

This study reports changes in the patterns of practice of definitive radiotherapy for cervical cancer in Japan since 1995 by comparing 3 patterns of care surveys. There has been a significant trend toward use of concurrent chemotherapy consistent with randomized trial data. External beam radiation has became progressively more standardized. Intracavitary brachytherapy, however, still has not reached consistent levels of quality.

Purpose: The patterns of care study (PCS) of radiotherapy for cervical cancer in Japan over the last 10 years was reviewed.

Methods and Materials: The Japanese PCS working group analyzed data from 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with definitive radiotherapy in Japan.

Results: Patients in the 2001–2003 survey were significantly younger than those in the 1999–2001 study ($p < 0.0001$). Histology, performance status, and International Federation of Gynecology and Obstetrics stage were not significantly different among the three survey periods. Use of combinations of chemotherapy has increased significantly during those periods (1995–1997, 24%; 1999–2001, 33%; 2003–2005, 54%; $p < 0.0001$). The ratio of patients receiving concurrent chemotherapy has also dramatically increased (1995–1997, 20%; 1999–2001, 54%; 2003–2005, 83%; $p < 0.0001$). As for external beam radiotherapy (EBRT), the application rate of four-field portals has greatly increased over the three survey periods (1995–1997, 2%; 1999–2001, 7%; 2003–2005, 21%; $p < 0.0001$). In addition, the use of an appropriate beam energy for EBRT has shown an increase (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). As for intracavitary brachytherapy (ICBT), an iridium source has become increasingly popular (1995–1997, 27%; 1999–2001, 42%; 2003–2005, 84%; $p < 0.0001$). Among the three surveys, the ratio of patients receiving ICBT (1995–1997, 77%; 1999–2001, 82%; 2003–2005, 78%) has not changed. Although

Reprint requests to: Natsuo Tomita, M.D., Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan. Tel: (81) 52-762-6111; Fax: (81) 52-752-8390; E-mail: ntomita@aichi-cc.jp

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follow-up was inadequate in each survey, no significant survival differences were observed ($p = 0.36$), and rates of late Grade 3 or higher toxicity were significantly different ($p = 0.016$). **Conclusions:** The Japanese PCS has monitored consistent improvements over the past 10 years in the application of chemotherapy, timing of chemotherapy, and EBRT methods. However, there is still room for improvement, especially in the clinical practice of ICBT. © 2011 Elsevier Inc.

Keywords: Cervix, Chemotherapy, Japan, Patterns of care study, Radiotherapy

Introduction

In Japan, the number of uterine cervical cancers decreased from the 1980s to 2000 but has been steadily increasing since then (1). The age-adjusted mortality rate due to cervical cancer has also shown an increase, especially in the younger generation in Japan (3). Radiation therapy is established as an integral component for cervical cancer. Over the past 10 years, some changes have occurred in the cervical cancer radiotherapy policy in Japan. Given the increases in cervical cancer and age-adjusted mortality rates, to optimally treat Japanese cervical cancer patients, it is important to accurately delineate intrinsic changes taking place in the national practice process of radiotherapy for cervical cancer in Japan. The patterns of care study (PCS) (2) initially surveyed radiotherapy practice in the United States. In the United States, PCS has been conducted for more than 30 years, and the structure, process, and outcomes of radiotherapy, as well as various problems in clinical practice, have been identified for cervical cancer (4, 5). The Japanese PCS began in 1996 and used the same methods (6). We previously reported Japanese PCS results for radiotherapy practice in cervical cancer patients treated in 1995–1997 and 1999–2001 (7, 8). We report here the corresponding results for 2003–2005, and the changes in radiotherapy practice that occurred over the years from the 1995–1997, 1999–2001, and 2003–2005 survey periods are also examined.

Methods and Materials

Between 2006 and 2008, the Japanese PCS working group conducted a third national survey of patients with uterine cervical cancer treated with radiotherapy. Patients who were eligible for the survey (*1*) had carcinoma, (*2*) were treated between January 2003 and December 2005, and (*3*) had no distant metastasis, (*4*) no prior or concurrent malignancy, (*5*) no gross para-aortic lymph node metastasis, and (*6*) no previous pelvic radiotherapy. Sixty-one of 640 institutions were selected for this survey by using a stratified two-staged cluster sampling method. Before the random sampling, all institutions were divided into four groups. Institutions were classified by type and number of patients treated with radiotherapy. The Japanese PCS working group stratified Japanese institutions as A1, academic institutions treating ≥430 patients annually; A2, academic institutions treating <430 patients; B1, nonacademic institutions treating ≥130 patients annually; and B2, nonacademic institutions treating <130 patients. Detailed criteria for stratification have been shown elsewhere (6). The Japanese PCS surveyors performed on-site chart reviews at each participating facility, using an originally developed database format for cervical cancer. Data collection included patient characteristics, details of the pretreatment workup, therapeutic information, and treatment outcome. The Japanese PCS collected clinical data for 487 patients with cervical cancer, who were treated with radiotherapy from 61 institutions. In this study, 285 patients treated with radiotherapy without planned surgery were analyzed. These included 114 patients from A1 institutions, 87 patients from A2 institutions, 50 patients from B1 institutions, and 34 patients from B2 institutions. There were unknown and missing data in the tables because no valid data were found in the given resources.

In addition, the current study compared data for three Japanese PCS surveys of 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with radiotherapy with curative intent. Methods for the 1995–1997 and 1999–2001 PCS were the same as those for the 2003–2005 study. Ratios were calculated without unknown or missing data. Statistical significance was tested using the chi-square test.

Results

Patient characteristics in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

Table 1 shows characteristics of the 285 patients in the 2003–2005 survey and changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods. The ages of the analyzed cohorts were significantly different among the three survey periods ($p < 0.0001$). The ages of the analyzed cohort were not different between the 1995–1997 and 1999–2001 surveys ($p = 0.34$) but were significantly different between the 1999–2001 and 2003–2005 surveys ($p < 0.0001$). Karnofsky performance status (KPS), histology, and International Federation of Gynecology and Obstetrics (FIGO) stages were not significantly different among the three survey periods, as shown in Table 1.

EBRT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, EBRT was performed in 283 patients (99%). Major treatment parameters for pelvic EBRT in the 2003–2005 survey are shown in Table 2. Treatment parameters in the 2003–2005 survey other than those shown in Table 2 are as follows. In 220 cases (78%), multileaf collimators were used to shape the portals. For 265 patients (94%), the planning target volume included the whole pelvic region. The upper border of the pelvic field was at level of the L4–L5 interspace in 245 of the 265 patients (92%). Only 6 patients (2%) received extended field radiotherapy that included the para-aortic region. The median radiation treatment time was 6.0 weeks (range, 1.1–13.0 weeks). The median radiation treatment time exceeded 8 weeks in 7 patients (3%).

Table 1 Patient and tumor characteristics of patients with uterine cervical cancer treated with radiotherapy in each surveillance period

Characteristic	No. of patients (%)			
	1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Age (years)				<0.0001
Range	28–94	26–100	25–95	
Median	70	71	67	
KPS				0.21
≤70	133 (23)	64 (21)	52 (18)	
80–90	421 (72)	217 (72)	193 (68)	
100	28 (5)	21 (7)	40 (14)	
Unknown/missing	9 (–)	22 (–)	0 (–)	
Histology				0.99
Squamous cell	554 (95)	300 (94)	257 (92)	
Adenocarcinoma	23 (4)	14 (4)	14 (5)	
Adenosquamous cell	4 (1)	4 (1)	5 (2)	
Other	4 (1)	2 (1)	3 (1)	
Unknown/missing	6 (–)	4 (–)	6 (–)	
FIGO stage				0.89
I	57 (10)	43 (14)	27 (10)	
II	171 (29)	102 (34)	85 (30)	
III	280 (48)	122 (40)	132 (46)	
IVA	75 (13)	35 (12)	41 (14)	
Other	5 (1)	0 (0)	0 (0)	
Unknown/missing	3 (–)	22 (–)	1 (–)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KPS = Karnofsky performance status.

Changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods are also shown in Table 2. The ratio of appropriate EBRT beam energy levels of more than or equal to 10 MV showed a tendency to increase over the three surveys (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). In addition, application of four-field portals greatly increased over the three surveys ($p < 0.0001$). Use of a midline block, single-daily fraction doses, and total point A doses were not significantly different among the three survey periods.

ICBT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

No patient surveyed received interstitial brachytherapy in the 2003–2005 survey. Fifty-nine patients (27%) received ICBT at another facility. Details of ICBT in the 2003–2005 survey are shown in Table 3. In most patients, all high-dose-rate ICBT (HDR-ICBT) procedures (applicator insertion, radiograph generation, and treatment) were performed in the same room, but these data for dose calculations for the rectum and bladder and the ICBT method showed a considerable rate of unknown or missing data.

Changes in ICBT practice over the years are also shown in Table 3. A ratio of Ir-192 source showed a significant increase among the three surveys ($p < 0.0001$). The number of patients who received no supportive medication before or during the applicator insertion significantly decreased over the three survey periods ($p < 0.0001$), but conscious sedation was still used for a few patients. The use of ICBT, dose rate, method of ICBT, and single-daily fraction dose were not different among the three survey periods. The use of *in vivo* dosimetry and International Commission on Radiation Units and Measurements (ICRU) report 38 calculations for bladder and rectum were not different among the three survey periods, although these data also showed an appreciable rate of unknown or missing data.

Chemotherapy in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, chemotherapy was given to 149 patients (54%), as shown in Table 4. Neoadjuvant chemotherapy was given to 16 patients before they received radiation therapy (11%), and 124 patients (83%) were treated with concurrent chemoradiation (CCRT). Weekly cisplatin was the agent most frequently used with CCRT (45%), and cisplatin was the most common agent in CCRT (55%) regimens.

Changes in chemotherapy practice over the years are also shown in Table 4. Application of chemotherapy significantly increased over the three survey periods ($p < 0.0001$). In addition, concurrent use of chemotherapy with radiotherapy has dramatically increased ($p < 0.0001$). On the other hand, the ratio of neoadjuvant chemotherapy in the most recent survey (2003–2005, 11%) decreased compared to those of 1995–1997 (58%) and 1999–2001 (50%).

Comparison of outcomes and toxicity between the 1995–1997, 1999–2001, and 2003–2005 surveys

Overall survival rates of patients in each survey are shown in Figure 1. Two-year survival rates in the 1995–1997, 1999–2001,

Table 2 Treatment parameters of pelvic external beam radiotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

	No. of patients (%)			
Parameters	1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Beam energy				0.064
Co-60 and 3–5 MV	96 (17)	32 (11)	20 (7)	
6–9 MV	82 (14)	45 (15)	30 (11)	
10–14 MV	338 (59)	220 (71)	191 (70)	
≥15 MV	45 (8)	9 (3)	31 (11)	
Other	10 (2)	0 (0)	1 (0)	
Unknown/ missing	20 (–)	2 (–)	12 (–)	
Technique				<0.0001
AP-PA	560 (98)	269 (87)	205 (75)	
Four-field box	11 (2)	21 (7)	57 (21)	
Other	1 (0)	17 (6)	11 (4)	
Unknown/ missing	19 (–)	1 (–)	12 (–)	
Midline block				0.56
Yes	386 (69)	215 (75)	186 (69)	
No	171 (31)	72 (25)	82 (31)	
Unknown/ missing	34 (–)	1 (–)	17 (–)	
Daily fraction size (Gy)				0.10
<1.8	13 (2)	25 (8)	3 (1)	
1.8	259 (45)	135 (44)	142 (51)	
>1.8 to <2	0 (0)	2 (1)	8 (3)	
2	299 (52)	137 (45)	120 (43)	
>2	3 (1)	6 (2)	4 (2)	
Unknown/ missing	17 (–)	3 (–)	8 (–)	
Total point A dose (Gy)				0.39
0–20	23 (8)	13 (5)	23 (9)	
20–30	42 (14)	40 (14)	58 (21)	
30–40	119 (38)	121 (42)	128 (47)	
40–50	57 (18)	62 (22)	46 (11)	
>50	69 (22)	49 (17)	17 (17)	
Unknown/ missing	17 (–)	39 (–)	12 (–)	
Median	32.2	32.4	32.4	

Abbreviations: AP-PA = opposing anteroposterior-posteroanterior; EBRT = external beam radiotherapy.

and 2003–2005 surveys were 83.4%, 78.4%, and 80.5%, respectively, with a median follow-up of only 2.4, 1.4, and 1.7 years, respectively, in the three studies. These differences did not reach a statistically significant level (p = 0.36).

Rates of developing late Grade 3 or higher toxicity of cervical cancer patients surveyed in each survey are shown in Figure 2. Two-year rates of developing late Grade 3 or higher toxicity in the 1995–1997, 1999–2001, and 2003–2005 surveys were 4.4%, 2.3%, and 8.5%, with a median follow-up of only 2.3, 1.4, and 1.7 years, respectively, in the three studies. Rates of late toxicity were significantly different (p = 0.016).

Discussion

The current study showed that, in Japan, a significant increase was observed in the rate of patients who received chemotherapy over the three periods of 1995–1997, 1999–2001, and 2003–2005. Several RCTs conducted in the 1990s demonstrated that CCRT reduced mortality risk in cervical cancer patients compared with radiotherapy alone (9). The current study showed that a combination of chemotherapy with radiotherapy has become widely used in Japan, similar to the change in the United States in the late 1990s. Concurrent use of chemotherapy also significantly increased over the three survey periods. Our study suggests that more appropriate management of uterine cervical cancer has been adopted in Japan. On the other hand, more than half of the patients (125 patients did not receive chemotherapy; and 25 of the patients who did receive chemotherapy did not receive CCRT) were not treated with CCRT in the 2003–2005 survey, although not all of these patients needed CCRT. Some Japanese physicians remain cautious about employing CCRT as a standard treatment for two reasons. The first reason concerns the feasibility of using the standard chemotherapy of weekly cisplatin concurrently with radiotherapy. Several reports have found Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 dosages of cisplatin might not be feasible for Japanese patients (10). The second reason is that there are limited data for CCRT using HDR-ICBT. A large amount of data concerning excellent outcomes and acceptable toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data are limited (11). Therefore, a prospective study (Japanese Gynecologic Oncology Group study 1066) was undertaken to evaluate toxicities and outcomes in patients treated with CCRT by using the standard dosage/schedule of cisplatin and the standard Japanese radiotherapy dosage schedules for HDR-ICBT (12). On the other hand, whereas several RCTs revealed the negative therapeutic value of neoadjuvant chemotherapy in the mid-1990s, more than 10% of patients were still treated with this strategy during the most recent survey period. However, the current study showed that the ratio of neoadjuvant chemotherapy decreased in the recent survey (2003–2005, 11%) compared to those in the 1995–1997 (58%) and 1999–2001 (50%) surveys. Cisplatin was the agent most commonly used in CCRT (55%) in the 2003–2005 survey. Previous recommendations have been limited to platinum-based chemoradiotherapy, but a recently released individual patient data meta-analysis (13) has shown a significant benefit also associated with non-platinum regimens, specifically those containing 5-fluorouracil and/or mitomycin-C, although those results are not based on a direct comparison. Therefore, detailed information about chemotherapy regimens other than cisplatin will need to be evaluated in future PCS surveys of radiotherapy for cervical cancer.

The current study showed that the four-field technique was gradually applied more frequently over the three survey periods and that the ratio of the four-field technique during the 2003–2005 period was 21%. However, most patients were still treated with the opposing anteroposterior (AP-PA) technique in

Table 3 Details of intracavitary brachytherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameter	No. of patients (%)			p
	1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	
ICBT given				0.66
Yes	454 (77)	265 (82)	222 (78)	
No	132 (23)	58 (18)	63 (22)	
Unknown/missing	5 (–)	1 (–)	0 (–)	
Dose rate				0.47
HDR	386 (89)	215 (89)	205 (93)	
LDR	37 (9)	27 (11)	13 (6)	
Other	10 (2)	0 (0)	2 (1)	
Unknown/missing	21 (–)	23 (–)	65 (–)	
Source				<0.0001
Ir-192	113 (27)	102 (42)	183 (84)	
Co-60	269 (64)	112 (46)	23 (11)	
Cs-137	33 (8)	21 (9)	12 (5)	
Ra-226	9 (2)	7 (3)	0 (0)	
Unknown/missing	33 (–)	23 (–)	67 (–)	
Method of ICBT				0.65
Tandem plus vaginal applicator	352 (87)	202 (83)	190 (89)	
Tandem only	30 (8)	26 (11)	14 (7)	
Vaginal applicator	22 (5)	16 (6)	6 (3)	
Others	0 (0)	0 (0)	3 (1)	
Unknown/missing	50 (–)	21 (–)	9 (–)	
Applicator				0.025
Rigid	NA	166 (72)	158 (85)	
Nonrigid	NA	66 (28)	27 (15)	
Unknown/missing	NA	33 (–)	100 (–)	
In vivo dosimetry: bladder				0.73
Yes	NA	8 (4)	9 (5)	
No	NA	207 (96)	171 (95)	
Unknown/missing	NA	50 (–)	105 (–)	
In vivo dosimetry: rectum				0.24
Yes	NA	71 (33)	75 (41)	
No	NA	145 (67)	108 (59)	
Unknown/missing	NA	49 (–)	102 (–)	
ICRU 38: bladder				0.12
Yes	NA	48 (25)	57 (35)	
No	NA	146 (75)	106 (65)	
Unknown/missing	NA	71 (–)	122 (–)	
ICRU 38: rectum				0.38
Yes	NA	65 (34)	68 (40)	
No	NA	128 (66)	104 (60)	
Unknown/missing	NA	72 (–)	113 (–)	
Preparation				<0.0001
None	199 (53)	90 (54)	33 (19)	
NSAIDs administered orally/rectally	107 (28)	68 (41)	86 (49)	
IV conscious sedation	29 (8)	5 (3)	7 (4)	
Others	2 (1)	3 (2)	49 (28)	
Unknown/missing	117 (–)	99 (–)	110 (–)	
All procedures performed in the same room*				0.58
Yes	NA	167 (94)	157 (92)	
No	NA	11 (6)	13 (8)	
Unknown/missing	NA	37 (–)	115 (–)	
Each fraction was planned*				0.16
Yes	NA	159 (76)	157 (84)	
No	NA	49 (24)	30 (16)	
Unknown/missing	NA	7 (–)	98 (–)	

(*continued on next page*)

Table 3 *(continued)*

Parameter	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Single-point A dose of HDR-ICBT (cGy)				<0.0001
0–499	16 (5)	43 (20)	14 (7)	
500–599	100 (33)	79 (37)	59 (29)	
600–699	145 (47)	48 (22)	123 (59)	
700–799	43 (14)	15 (7)	10 (5)	
>800	2 (1)	2 (1)	1 (1)	
Unknown/missing	21 (–)	28 (–)	65 (–)	
Median	600	524	600	
Total point A dose of HDR-ICBT (Gy)				<0.0001
0–10	4 (1)	5 (3)	6 (3)	
10–20	80 (26)	58 (31)	71 (34)	
20–30	145 (48)	113 (61)	127 (61)	
30–40	77 (25)	8 (4)	4 (2)	
>40	0 (0)	1 (0)	0 (0)	
Unknown/missing	21 (–)	24 (–)	64 (–)	
Median	24.0	20.3	24.0	

Abbreviations: HDR = high-dose rate; ICBT = intracavitary brachytherapy; ICRU = International Commission on Radiation Units and Measurements; LDR = low-dose rate; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory inflammatory drugs.
* A total of 222 patients were treated with HDR-ICBT.

Japan, and rates of the use of the four-field technique remained low during the latest period. According to a report of the status of Japanese radiation oncology, one of the problems for the national practice process of radiotherapy in Japan was structural immaturity, especially in terms of personnel (14). Results of our study indicated that radiotherapy characteristics are still developing in Japan. The current study also revealed a change in the beam energy used for radiotherapy in Japan over the three survey periods. Only 7% of the patients were treated with Co-60 and 3 to 5 MV in 2003–2005, whereas these energies were used in 17% of patients in 1995–1997 and 11% of patients in 1999–2001. In addition, the use of appropriate beam energies of 10 to 14 MV and ≥15 MV increased over the three survey periods. In conjunction with the increased numbers of full-time equivalent radiation oncologists in both academic and nonacademic institutions (15),

Table 4 Details of chemotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameters	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Chemotherapy given				<0.0001
Yes	140 (24)	104 (33)	149 (54)	
No	434 (76)	213 (67)	125 (46)	
Unknown/missing	17 (–)	7 (–)	11 (–)	
Timing*				<0.0001
Neoadjuvant	81 (58)	52 (50)	16 (11)	
Concurrent	28 (20)	56 (54)	124 (83)	
Adjuvant	31 (22)	15 (14)	34 (23)	
Agent†				NA
CDDP weekly	NA	NA	49 (45)	
CDDP daily	NA	NA	5 (5)	
CDDP plus 5-FU	NA	NA	6 (5)	
Others	NA	NA	49 (45)	
Unknown/missing	NA	NA	15 (–)	

Abbreviations: 5-FU = 5-fluorouracil; CDDP = cisplatin; NA = not applicable.
* Some patients overlap in the timing column.
† The indicated agent was used for patients who received concurrent chemotherapy.

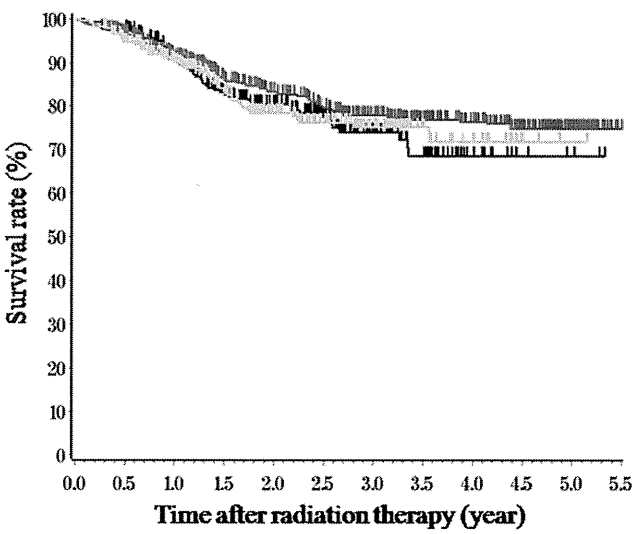

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

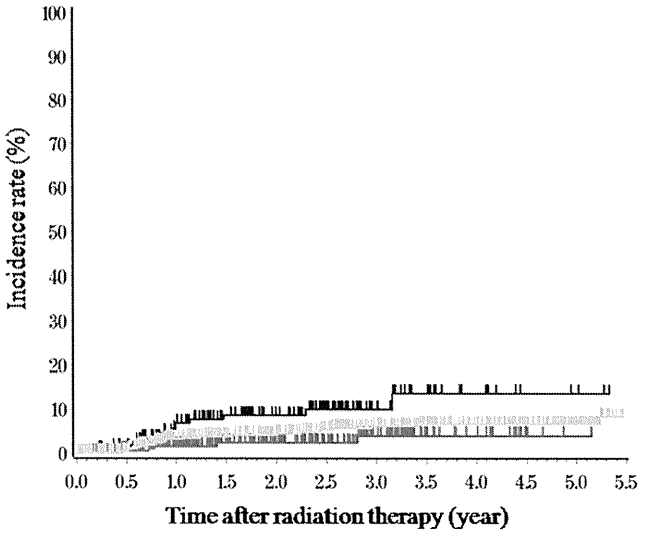

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

Japanese cervical cancer patients are increasingly undergoing more appropriate methods.

The ratio of patients receiving ICBT did not increase over the three surveys. A considerable number of patients, 22%, were still not given ICBT during 2003–2005, and the application rate was lower in Japan than in the United States (4, 5). Therefore, ICBT should be applied more routinely for cervical cancer patients treated with definitive radiotherapy in Japan. One reason for the fact that some patients were not given ICBT might have been insufficient equipment, because 27% of patients received ICBT at another institution compared with 8.5% in the United States (16). The use of Ir-192 in 2003–2005 increased significantly compared with that in 1995–1997 and 1999–2001. The rapid increase in the use of Ir-192 might have been due to the result of the Japanese Society for Therapeutic Radiology and Oncology recommendation in the early 2000s that stated Co-60 should be avoided as a remote afterloading brachytherapy source in Japan because of source attenuation consistent with age. The American Brachytherapy Society (ABS) made a number of recommendations regarding HDR-ICBT techniques (17). Doses to the rectum were more often determined by using a dosimeter than by ICRU 38 reference point calculations. In fact, many studies showed that late rectal complications can be predicted by calculated doses at the ICRU 38 reference points (18). According to the ABS survey, rectal/bladder doses were evaluated in 80% or more patients at U.S. institutions, where HDR radiation was performed (19). However, our study showed that doses to the rectum and bladder in ICBT were evaluated, at most, in 40% of patients in Japan, and this status has significant scope for further improvement. Because accurate insertion can hardly be achieved if patients experience discomfort in ICBT, the ABS also recommends conscious sedation for HDR-ICBT applicator insertions (17). The current study showed that the number of patients who received no supportive medication before or during the applicator insertion significantly decreased, but conscious sedation was still used for a few patients. Although there are some limitations to the interpretation of these data due to an appreciable rate of unknown or missing data, we believe that additional improvements in the management of ICBT are still needed.

The current study also showed that patients' ages in the 1999–2001 survey were significantly different than those in the 2003–2005 survey, and the median age of 71 years old in the 2003–2005 survey was younger than that of the median age of 67 years old in the 1999–2001 survey. We think this may be due to the recent change in the age-specific incidence rate of cervical cancer in Japan. The age-specific incidence rate of cervical cancer in women over 40 years old has fallen gradually since the 1980s, while that in patients under 40 has gradually increased (21). Thus, the percentage of younger patients treated with radiotherapy may have increased. Konno *et al.* (22) organized the critical public health issues about cervical cancer in Japan in their cervical cancer working group report. In Japan, a national program for screening of cervical cancer was enacted in 1982. However, Organization for Economic Cooperation and Development data showed high rates of cervical cancer screening coverage in the United States and Europe but low coverage in Japan (23.4%) (20). With regard to cervical cancer prevention in Japan, in 1983, the government passed a Health and Medical Service Law for the Aged, leaving screening up to regional governments. A human papilloma virus vaccine was licensed in 2009 in Japan.

No significant survival improvement in patient outcome was observed among the three surveys. On the other hand, rates of late toxicity were significantly different in each study. One possible cause for these differences was the dramatic increase in the use of CCRT over the three survey periods. However, the current study has limitations in terms of outcome and toxicity analysis because of an inadequate follow-up time and significant variations in follow-up information according to institutional stratification (6). Therefore, we cannot draw any conclusions about Japanese radiotherapy practice in cervical cancer from these outcome and toxicity data.

Conclusions

In conclusion, we reported the status of definitive radiotherapy for uterine cervical cancer in Japan between 2003 and 2005 and examined the changes over the years in radiotherapy practice in the 1995–1997, 1999–2001, and 2003–2005 survey periods. By comparing the results of previous surveys with those of the 2003–2005 PCS survey, we delineated the changes in the process of care for cervical cancer patients treated with radiotherapy in Japan. Study data indicate a significant trend toward a combination of chemotherapy and concurrent use of chemotherapy and radiation therapy due to the adoption of recommendations found in RCTs. EBRT conditions such as beam energy and technique were gradually standardized to more appropriate methods over the three periods. Regarding ICBT, the patterns of both clinical procedure and quality assessment have still not reached sufficient quality. We believe that the three surveys of Japanese patterns of care for cervical cancer clearly show distinct improvements, while several problems remain to be resolved.

References

1. Ohno Y, Nakamura T, Murata K, *et al.* Prediction of cancer incidence in Japan. In: Oshima A, Kuroishi T, Tajima K, editors. Cancer statistics—2004. Tokyo: Shinohara Shuppan; 2004. p. 201–207.

2. Hanks GE, Coia LR, Curry J. Patterns of care studies: past, present, and future. *Semin Radiat Oncol* 1997;7:97–100.
3. Yang L, Fujimoto J, Qiu D, *et al.* Trends in cancer mortality in Japanese adolescents and young adults aged 15-29 years, 1970-2006. *Ann Oncol* 2009;20:758–766.
4. Eifel PJ, Moughan J, Owen J, *et al.* Patterns of radiotherapy practice for patients with squamous carcinoma of the uterine cervix: Patterns of care study. *Int J Radiat Oncol Biol Phys* 1999;43:351–358.
5. Eifel PJ, Moughan J, Erickson B, *et al.* Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: A patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;60: 1144–1153.
6. Teshima T. Patterns of care study in Japan. *Jpn J Clin Oncol* 2005;35: 497–506.
7. Toita T, Nakamura K, Uno T, *et al.* Radiotherapy for uterine cervical cancer: Results of the 1995–1997 patterns of care process survey in Japan. *Jpn J Clin Oncol* 2005;35:139–148.
8. Toita T, Kodaira T, Shinoda A, *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999-2001): Patterns of care study in Japan. *Int J Radiat Oncol Biol Phys* 2008;70:788–794.
9. Rose PG, Bundy BN, Watkins EB, *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–1153.
10. Watanabe Y, Nakai H, Shimaoka M, *et al.* Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: A phase I study in Japanese patients with cancer of the uterine cervix. *Int J Clin Oncol* 2006;11:309–313.
11. Toita T, Kato S, Niibe Y *et al.* Prospective multi-institutional study of definitive radiotherapy with high-dose rate intracavitary brachytherapy in patients with nonbulky (<4 cm) stage I, II uterine cervical cancer (JAROG0401/JROSG04–2). *Int J Radiat Oncol Biol Phys.* In press.
12. Toita T, Kato S, Ishikura S, *et al.* Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): A cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer. *Int J Clin Oncol.* In press.
13. Cochrane Gynaecological Cancer Group. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: Individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010;1: CD008285. Review.
14. Nakano T. Status of Japanese radiation oncology. *Radiat Med* 2004; 22:17–19.
15. Ogawa K, Nakamura K, Sasaki T, *et al.* Radical external beam radiotherapy for clinically localized prostate cancer in Japan: Changing trends in the patterns of care process survey. *Int J Radiat Oncol Biol Phys.* In press.
16. Erickson B, Eifel P, Moughan J, *et al.* Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): A patterns of care study. *Int J Radiat Oncol Biol Phys* 2005;63: 1083–1092.
17. Nag S, Erickson B, Thomadsen B, *et al.* The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48: 201–211.
18. Toita T, Kakinohana Y, Ogawa K, *et al.* Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;56:1344–1353.
19. Nag S, Orton C, Young D, *et al.* The American brachytherapy society survey of brachytherapy practice for carcinoma of the cervix in the United States. *Gynecol Oncol* 1999;73:111–118.
20. Armesto Garcia S, Lapetra Gil ML, Wei L, *et al. Members of the Health Care Quality Indicators (HCQI) Expert Group.* Health Care-Quality Indicators Project 2006 Data Collection Update Report. OECD HealthWorking Papers No. 29, DELSA/HEA/WD/HWP. Paris: Organization for Economic Co-operation and Development; 2007.
21. Center for Cancer Control and Information Services, National Cancer Center, Japan. [In Japanese]. Available at: http://ganjoho.ncc.go.jp/professional/statistics/statistics.html. Accessed November 13, 2011.
22. Konno R, Sagae S, Yoshikawa H, *et al.* Cervical Cancer Working Group report. *Jpn J Clin Oncol* 2010;40(Suppl 1):i44–i50.

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Changing trend in the patterns of pretreatment diagnostic assessment for patients with cervical cancer in Japan

Natsuo Tomita [a,*], Takafumi Toita [b], Takeshi Kodaira [a], Atsunori Shinoda [c], Takashi Uno [d], Hodaka Numasaki [e], Teruki Teshima [e], Michihide Mitsumori [f]

[a] Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Japan
[b] Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan
[c] Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan
[d] Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan
[e] Department of Medical Physics and Engineering, Graduate School of Medicine, Osaka University, Suita, Japan
[f] Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine Kyoto University, Kyoto, Japan

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ABSTRACT

Objective. Cancer staging systems should be responsive to the development of diagnostic tools. The International Federation of Gynecology and Obstetrics (FIGO) cervical cancer guidelines were modified in 2009 regarding the pretreatment assessment. We report the recent Japanese patterns of pretreatment workup for cervical cancer.

Methods. The Japanese Patterns of Care Study (PCS) working group analyzed the pretreatment diagnostic assessment data of 609 patients with cervical cancer treated with definitive radiotherapy in the two survey periods (1999–2001, 324; 2003–2005, 285) in Japan. Sixty-one of 640 institutions were selected for this survey using a stratified two-staged cluster sampling method.

Results. The use of optional examinations in the latest FIGO guidelines such as intravenous urography, cystoscopy, and proctoscopy was gradually decreasing. Surgical staging was rarely performed in either survey period. Computed tomography (CT) and magnetic resonance imaging (MRI) were widely used, and MRI has become increasingly prevalent even between the two survey periods. Primary lesion size and pelvic lymph node status was evaluated by CT/MRI for most patients in both surveys.

Conclusions. The use of CT/MRI that is encouraged in the latest FIGO staging guidelines already replaced intravenous urography, cystoscopy, and proctoscopy in Japan. Japanese patients received the potential benefit of CT/MRI because prognostic factors such as primary lesion size and pelvic lymph node status were evaluated by these modalities. The use of cystoscopy and proctoscopy should be continuously monitored in the future PCS survey because only CT/MRI could lead to the stage migration for patients on suspicion of bladder/rectum involvement on CT/MRI.

Introduction

Radiation therapy is established as an integral component of cervical cancer. Accurate understanding of the cancer's extent is necessary for appropriate radiation treatment planning. In the first place, precise cancer staging is essential to predict prognosis and make appropriate decision regarding the primary treatment. The International Federation of Gynecology and Obstetrics (FIGO) provided a global staging system for gynecologic cancers and made several modifications over time. The previous FIGO guidelines recommended that staging be based on physical examination, colposcopy, hysteroscopy, lesion biopsy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the chest and skeleton. Of these, findings of optional examinations such as lymphangiography, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are of value for planning therapy, but, because these are not generally available and the interpretation of results is variable, the findings of such studies should not be the basis for changing the clinical staging [1]. However, cancer staging systems should be based on, and updated according to, the latest available knowledge, implying that they should be responsive and adaptive to scientific developments [2]. Thus, the FIGO guidelines for cervical cancer were modified in January 2009. In the updated guidelines, radiological tumor volume and parametrial invasion should be recorded for those institutions with access to MRI/CT [3]. In addition, other investigations such as cystoscopy, proctoscopy, and intravenous urography were classified as optional and no longer mandatory [3].

* Corresponding author at: Department of Radiation Oncology, Aichi Cancer Center Hospital, 1–1 Kanokoden, Chikusaku, Nagoya 464–8681, Japan. Fax: +81 52 752 8390.
E-mail address: ntomita@aichi-cc.jp (N. Tomita).

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The Patterns of Care study (PCS) initially surveyed radiotherapy practice in the United States, and the structure, process, and outcomes of radiotherapy, as well as various problems in clinical practice, have been identified for cervical cancer [4,5]. The Japanese PCS began in 1996 and used the same methods [6]. To accurately evaluate the cancer stage and optimally treat Japanese cervical cancer patients, it is important to accurately delineate the intrinsic changes in the patterns of pretreatment workup for cervical cancer in Japan. We previously reported the care process patterns in pretreatment diagnostic assessment and staging for patients with cervical cancer treated in 1999–2001 [7]. We report here the corresponding results for 2003–2005, and the changes over the years in pretreatment work-up from the 1999–2001 to 2003–2005 survey periods are examined.

Methods and materials

Between 2006 and 2008, the Japanese PCS 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 2003 and December 2005, (3) no distant metastasis, (4) no prior or concurrent malignancy, (5) no gross paraaortic lymph node metastasis, and (6) no previous pelvic radiotherapy. Sixty-one of 640 institutions were selected for this 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 patients treated with radiotherapy. The Japanese PCS stratified 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 detailed criteria for stratification have been shown elsewhere [6]. The Japanese PCS surveyors performed on-site chart reviews at each participating facility using an originally developed database format for cervical cancer. Data collection included patient characteristics, details of the pretreatment workup, therapeutic information (e.g., radiotherapy, chemotherapy, and surgery), and treatment outcome. The Japanese PCS collected clinical data on 487 patients with uterine cervical cancer who were treated with radiotherapy from 61 institutions. In this study, 285 patients treated by radiotherapy without planned surgery were analyzed. These included 114 patients from A1 institutions, 87 patients from A2 institutions, 50 patients from B1 institutions, and 34 patients from B2 institutions. There were unknown and missing data in the tables because no valid data were found in the given resources.

The current study compared the pretreatment workup data of two Japanese PCS surveys with more than 600 patients (1999–2001, 324; 2003–2005, 285) with cervical cancer treated by radiotherapy with curative intent. The methods for the 1999–2001 Japanese PCS were the same as those for 2003–2005. Ratios were calculated without unknown or missing data. Statistical significance was tested using the chi-square test.

Results

Table 1 gives a comparison of the patient characteristics between the Japanese PCS 1999–2001 and 2003–2005 survey of cervical cancer patients treated with definitive radiotherapy. The ages of the analyzed cohort were significantly different in the 1999–2001 and 2003–2005 surveys ($p<0.0001$). Histology and FIGO stage were not significantly different in the two survey periods.

Table 2 shows a comparison of the performance rates of diagnostic procedures with a certain rate of unknown or missing data between the 1999–2001 and 2003–2005 surveys. Most patients underwent a chest X-ray in both the 1999–2001 and 2003–2005 surveys, but the ratio of patients who underwent a chest X-ray significantly decreased

Table 1
Patient and tumor characteristics of patients with uterine cervical cancer treated with radiotherapy in each surveillance period.

Characteristics	No. of patients (%)		
	1999–2001 (n=324)	2003–2005 (n=285)	p
Age (years)			<0.0001
Range	26–100	25–95	
Median	71	67	
Histology			0.84
Squamous cell	300 (94%)	257 (92%)	
Adenocarcionoma	14 (4%)	14 (5%)	
Adenosquamous cell	4 (1%)	5 (2%)	
Other	2 (1%)	3 (1%)	
Unknown/missing	4 (−)	6 (−)	
FIGO stage			0.13
I	43 (14%)	27 (10%)	
II	102 (34%)	85 (30%)	
III	122 (40%)	132 (46%)	
IVA	35 (12%)	41 (14%)	
Unknown/missing	22 (−)	1 (−)	

Abbreviations: KPS: karnofsky performance status, FIGO: International Federation of Gynecology and Obstetrics.

Table 2
Pretreatment diagnostic procedure in the 1999–2001 and 2003–2005 survey periods.

Parameters	No. of patients (%)		
	1999–2001 (n=324	2003–2005 (n=285)	p
Chest radiography			0.0002
Yes	241 (97%)	191 (88%)	
No	7 (3%)	25 (12%)	
Unknown/missing	76 (−)	69 (−)	
Intravenous urography			<0.0001
Yes	176 (72%)	86 (42%)	
No	68 (28%)	118 (58%)	
Unknown/missing	80 (−)	81 (−)	
Cystoscopy			0.0005
Yes	171 (74%)	123 (58%)	
No	60 (26%)	88 (42%)	
Unknown/missing	93 (−)	74(−)	
Proctoscopy			0.027
Yes	108 (49%)	70 (34%)	
No	114 (51%)	134 (66%)	
Unknown/missing	102 (−)	81 (−)	
Barium enema			0.098
Yes	24 (11%)	14 (7%)	
No	193 (89%)	200 (93%)	
Unknown/missing	107 (−)	71 (−)	
Lymphangiography			0.71
Yes	3 (1%)	16 (9%)	
No	241 (99%)	171 (91%)	
Unknown/missing	80 (−)	98 (−)	
Surgical Staging			0.042
Yes	3 (1%)	10 (4%)	
No	257 (99%)	241 (96%)	
Unknown/missing	64 (−)	34 (−)	
Abdominal CT			0.053
Yes	258 (95%)	247 (98%)	
No	14 (5%)	5 (2%)	
Unknown/missing	52 (−)	33 (−)	
Pelvic CT			0.75
Yes	286 (97%)	255 (98%)	
No	8 (3%)	5 (2%)	
Unknown/missing	30 (−)	25 (−)	
Pelvic MRI			0.021
Yes	246 (86%)	234 (92%)	
No	39 (14%)	19 (8%)	
Unknown/missing	39 (−)	32 (−)	
FDG-PET			0.34
Yes	1 (0%)	0 (0%)	
No	254 (100%)	229 (100%)	
Unknown/missing	69 (−)	56 (−)	

Abbreviations: NA: not applicable.

between the two survey periods. Intravenous urography and cystoscopy were performed in approximately three-quarters of patients in the 1999–2001 survey, but only half of patients underwent these examinations in the 2003–2005 survey. The ratio of the patients who underwent proctoscopy also significantly decreased between the two survey periods. On the whole, the ratio of patients who underwent barium enema and lymphangiography was low in both the 1999–2001 and 2003–2005 surveys. Surgical staging was rarely performed in either survey. Almost all patients underwent abdominal and pelvic CT in both surveys, and the ratios were not significantly different in the two survey periods. The ratio of the patients who underwent pelvic MRI was already high in the 1999–2001 survey, but this ratio further increased significantly. The ratio of patients underwent fluorodeoxyglucose positron emission tomography (FDG-PET) was 0% in both the 1999–2001 and 2003–2005 surveys.

Table 3 shows the performance status of the pretreatment evaluation for the primary lesion and pelvic lymph nodes with a certain rate of unknown or missing data. Primary lesion size was not evaluated for a certain percentage of patients in both the 1999–2001 and 2003–2005 surveys (11% and 15%, respectively). MRI was the most common modality for evaluating primary lesion size in both surveys. Median tumor size in the 2003–2005 survey was larger than that in the 1999–2001 survey. Especially, the ratio of tumors >60 mm increased between the two survey periods (13% to 24%). Pelvic nodal status was evaluated in almost all patients in both surveys. CT was most frequently used for the assessment of nodal status in both the 1999–2001 and 2003–2005 surveys (86% and 89%, respectively).

Discussion

The present study demonstrated that the use of optional examinations in the updated FIGO guidelines such as intravenous urography, cystoscopy, and proctoscopy is gradually decreasing in Japan, as well as in the United States [4,8,9]. In the 2000–2002 US study on the pretreatment evaluation of patients with stage IIB or lower disease, the rates for performing intravenous urography, cystoscopy, and proctoscopy were only 1, 16, and 17%, respectively [9]. The National Comprehensive Cancer Network (NCCN) guideline also states that cystoscopy and proctoscopy are optional examinations for the pretreatment assessment of cervical cancer patients with a disease stage of IB2 or higher [10]. On the other hand, this study showed that these optional procedures were still often performed in the patients surveyed in Japan, although these are older data than the FIGO guidelines update. We think that, although cystoscopy and proctoscopy are not necessary for the pretreatment assessment of cervical cancer patients with a disease stage of IB1 or lower, those examinations with biopsy are required for patients with a disease stage of IB2 or higher on suspicion of bladder/rectum involvement on CT or MRI because only CT/MRI could lead to the stage migration. Surgical staging and lymphangiography were rarely performed in either survey period. Eifel et al. reported that lymph node status was assessed by lymphangiography in 13.6%, and surgical evaluation in 12.2%, in the 1996–1999 US PCS [5], and other studies revealed that the performance of lymphangiography has also been decreasing recently [4,8,9]. Lagasse et al. found lymphangiography to be unreliable as a basis for treatment decisions [11]. As for surgical staging, although the FIGO Committee agrees on its potential important benefits, cost-effectiveness is still a matter of investigation and debate in a disease that can be cured with the same efficacy by other non-surgical treatment modalities [2]. In addition, there is increased morbidity when surgical node dissection is combined with subsequent radiation therapy [12]. We think that these procedures were replaced by CT or MRI before we started to survey the pretreatment workup data on the Japanese PCS. We predict that the performance rates of intravenous urography, cystoscopy, and proctoscopy will also decrease further, to be replaced by CT or MRI as in the United States. The ratio of patients who underwent a chest X-ray decreased significantly between the two survey periods. We presume that chest X-rays may also be replaced with chest CT, which can be done with abdominal and pelvic CT at one time, although we did not examine the performance status of chest CT in the two surveys.

This study demonstrated that CT and MRI were routinely performed in Japan in both survey periods. 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 [13,14]. Actually, the use of diagnostic imaging techniques to assess the size of the primary tumor is encouraged in the updated FIGO guidelines, and radiological tumor volume and parametrial invasion should be recorded for those institutions with access to MRI/CT [3]. This study showed that CT and MRI were already widely used before the revision of the FIGO guidelines in 2009, and pelvic MRI has become increasingly prevalent in Japanese clinical practice for cervical cancer even between the two survey periods. It is clear that the practice patterns of pretreatment workup in Japan and the USA are notable different than in areas which are less well developed. However, there is increasing availability of CT scanning in developing countries [9]. As CT and MRI techniques and training continue to develop, it is likely that accuracy for local staging will improve even further. Thus, we think that these cross-sectional diagnostic imaging will become more and more important to the pretreatment workup of cervical cancer. On the other hand, the use of CT or MRI is encouraged but still is not mandatory in the latest FIGO cervical cancer staging guidelines. As it stands now, it is important to record the staging method for each cervical cancer patient in any countries in order to avoid staging migration and to fairly compare treatment methods.

Primary lesion size was not evaluated for a certain percentage of patients in both surveys. As previously stated, since tumor size is an important prognostic factor for cervical cancer, it is necessary in clinical practice to evaluate the primary lesion size. MRI was the most common modality for evaluating primary lesion size in both surveys. On the other hand, a certain percentage of patients were had primary lesion size

Table 3
Pretreatment evaluation of the primary lesion and lymph node in the 1999–2001 and 2003–2005 survey periods.

Parameters	No. of patients (%)		
	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Evaluation of primary lesion size			0.30
Yes	246 (89%)	202 (85%)	
No	29 (11%)	36 (15%)	
Evaluation method of primary lesion*			NA
Inspection and palpation	20 (8%)	20 (10%)	
CT	53 (22%)	81 (40%)	
MRI	152 (62%)	145 (72%)	
US	21 (8%)	65 (32%)	
Diameter of primary lesion (mm)			0.008
0–10	3 (1%)	0	
10–20	12 (6%)	10 (5%)	
20–30	33 (15%)	28 (15%)	
30–40	54 (25%)	25 (14%)	
40–50	52 (24%)	47 (25%)	
60 <	27 (13%)	45 (24%)	
Unknown/missing	110 (−)	97 (−)	
Median	45 (0–100)	50 (15–107)	
Evaluation of pelvic lymph node			0.024
Yes	271 (97%)	224 (90%)	
No	8 (3%)	24 (10%)	
Unknown/missing	45 (−)	37 (−)	
Evaluation method of pelvic lymph node*			NA
CT	233 (86%)	209 (89%)	
MRI	37 (14%)	136 (58%)	
US	0	7 (3%)	
Others	1 (0%)	3 (1%)	

Abbreviations: US: ultrasonography, NA: not applicable.
* Some patients overlap in the 2003–2005 column.

evaluated by a physician's inspection and palpation, which is the method recommended by FIGO for evaluating primary lesion size. However, we think that tumor size assessment by physical examination has the potential to estimate tumor size incorrectly. Especially in clinical trials, we should evaluate primary lesion size by MRI because of its accuracy. Pelvic lymph node status was not evaluated for a certain percentage of patients in both surveys. Although the evaluation of lymph node status is an important prognostic factor and is essential for radiation treatment planning, it is not included in the FIGO guidelines despite improvements in imaging techniques. We believe that physicians should evaluate the lymph node status at least in institutions with access to MRI/CT because cervical cancer has a poor prognosis in the presence of lymph node metastasis, and this is particularly evident in early stage disease [15]. We think that pelvic CT is unnecessary for the pretreatment assessment of a cervical cancer patient when her MRI covers the whole pelvis, but if not, pelvic CT is also necessary. In addition, abdominal CT is required for the assessment of para-aortic lymph node status in the case of positive pelvic lymph node or a locally-advanced stage.

PET was rarely performed for cervical cancer in the two survey periods in Japan, although it has dramatically increased in the evaluation of patients with malignant neoplasms since approximately 2000 in Japan. This was due to the Japanese health insurance plan which did not cover cervical cancer at that time. Several studies showed the accuracy of PET for the staging of cervical cancer [16]. The Japanese health insurance plan started to cover cervical cancer in 2006. Its application is expected to increase in Japan in the next Japanese PCS survey for cervical cancer.

The limitation of our study was that several cases reviewed in this survey had unknown or missing data. The tables for pretreatment diagnostic tests in this study probably do not provide an accurate estimate of overall usage. Nevertheless, our results demonstrate that the FIGO-recommended workup including cystoscopy and proctoscopy is steadily decreasing in Japan, and there is a large discrepancy between the FIGO-recommended workup with cystoscopy and proctoscopy, and the actual tests being used.

In summary, the Japanese PCS describes the changes over the years in pretreatment work-up from the 1999–2001 to 2003–2005 survey periods in Japan. This study revealed that the FIGO recommended workup is steadily decreasing in Japan, while CT and MRI have been routinely performed. Patterns of pretreatment workup should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

Conflict of interest statement
None.

References

[1] Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006;95(Suppl 1):S43–S103.
[2] Odicino F, Pecorelli S, Zigliani L, et al. History of the FIGO cancer staging system. Int J Gynaecol Obstet 2008;101:205–10.
[3] Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet 2009;105:107–8.
[4] Montana GS, Hanlon AL, Brickner TJ, et al. Carcinoma of the cervix: patterns of care studies: review of 1978, 1983, and 1988–1989 surveys. Int J Radiat Oncol Biol Phys 1995;32:1481–6.
[5] Eifel PJ, Moughan J, Erickson B, et al. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. Int J Radiat Oncol Biol Phys 2004;60:1144–53.
[6] Teshima T. Patterns of care study in Japan. Jpn J Clin Oncol 2005;35:497–506.
[7] Toita T, Kodaira T, Uno T, et al. Patterns of pretreatment diagnostic assessment and staging for patients with cervical cancer (1999–2001): patterns of care study in Japan. Jpn J Clin Oncol 2008;38:26–30.
[8] Russell AH, Shingleton HM, Jones WB, et al. Diagnostic assessments in patients with invasive cancer of the cervix: a national patterns of care study of the American College of Surgeons. Gynecol Oncol 1996;63:159–65.
[9] Amendola MA, Hricak H, Mitchell DG, et al. Utilization of diagnostic studies in the pretreatment evaluation of invasive cervical cancer in the United States: results of intergroup protocol ACRIN 6651/GOG 183. J Clin Oncol 2005;23:7454–9.
[10] http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf 2009; volume 1.
[11] Lagasse LD, Creasman WT, Shingleton HM, et al. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. Gynecol Oncol 1980;9:90–8.
[12] Scheidler J, Hricak H, Yu KK, Subak L, Segal MR. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. JAMA 1997;278:1096–101.
[13] Toita T, Kakinohana Y, Shinzato S, et al. Tumor diameter/volume and pelvic node status assessed by magnetic resonance imaging (MRI) for uterine cervical cancer treated with irradiation. Int J Radiat Oncol Biol Phys 1999;43:777–82.
[14] Kodaira T, Fuwa N, Toita T, et al. Comparison of prognostic value of MRI and FIGO stage among patients with cervical carcinoma treated with radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:769–77.
[15] Aoki Y, Sasaki M, Watanabe M, et al. High-risk group in node-positive patients with stage IB, IIA, and IIB cervical carcinoma after radical hysterectomy and postoperative pelvic irradiation. Gynecol Oncol 2000;77:305–9.
[16] Grigsby PW, Siegel BA, Dehdashti F, et al. Posttherapy [^{18}F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. J Clin Oncol 2004;22:2167–71.

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ORIGINAL ARTICLE

Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): a cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer

Takafumi Toita · Shingo Kato · Satoshi Ishikura · Kayoko Tsujino · Takeshi Kodaira · Takashi Uno · Kazuo Hatano · Hideyuki Sakurai · Yuzuru Niibe · Tomoko Kazumoto · Tetsuo Nishimura · Ryo Kitagawa · Miki Fukutani · Masahiko Oguchi · Kenji Umayahara · Yasuyuki Hirashima · Yoichi Aoki · Ken Takizawa · and Disease Committee of Radiation Oncology, Japanese Gynecologic Oncology Group

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Abstract
Background To assess radiotherapy protocol compliance in a multi-institutional phase II study of concurrent chemoradiotherapy for patients with locally advanced cancer of the uterine cervix (JGOG1066).
Methods For study protocol development, various radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with cervical cancer treatment expertise. Quality assurance (QA) was also discussed and included in the protocol. A credentialing process was used to select institutions for participation in the study. Individual case reviews referring to 18 QA items were undertaken for each patient. Radiotherapy data were submitted to the Japanese Gynecologic Oncology Group (JGOG) data center and reviewed by the members of the radiotherapy committee. The QA evaluation was classed as per protocol, deviation, and violation.
Results Individual case reviews were performed on 69 of 72 patients entered in the study. In 24 patients (35%), there

T. Toita (✉)
Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho Okinawa 903-0215, Japan
e-mail: b983255@med.u-ryukyu.ac.jp

S. Kato
Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan

S. Ishikura
Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

K. Tsujino
Department of Radiation Oncology, Hyogo Cancer Center, Akashi, Japan

T. Kodaira
Department of Radiation Oncology, Aichi Cancer Center, Nagoya, Japan

T. Uno
Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan

K. Hatano
Division of Radiation Oncology, Chiba Cancer Center, Chiba, Japan

H. Sakurai
Proton Medical Research Center and Tsukuba University, Tsukuba, Japan

Y. Niibe
Department of Radiology, School of Medicine, Kitasato University, Sagamihara, Japan

T. Kazumoto
Department of Radiology, Saitama Cancer Center, Saitama, Japan

T. Nishimura
Division of Radiation Oncology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

R. Kitagawa
Department of Obstetrics and Gynecology, Kanto Medical Center NTT East Corporation, Tokyo, Japan

M. Fukutani
Kitasato University Research Center for Clinical Pharmacology, Tokyo, Japan

M. Oguchi
Department of Radiation Oncology, Cancer Institute Hospital, Tokyo, Japan

were no deviations for any QA items. There were also no deviations seen for 5 of the 18 items in 69 patients evaluated. Deviations of 64 QA items were seen in 45 cases, and violations were seen in 4 cases (4 items). The most common deviation concerned appropriate application for the external beam radiotherapy (EBRT) boost to involved nodes or parametrium (32 cases). The 4 violations were identified in the QA items regarding high-dose rate intracavitary brachytherapy.

Conclusions Radiotherapy protocol compliance was favorable except for the EBRT boost indications. The results of this study validate the quality of radiotherapy in JGOG1066, and indicate that the final analysis will provide meaningful results.

Keywords Carcinoma of the uterine cervix · Radiation therapy · Chemoradiotherapy · Intracavitary brachytherapy · High dose rate

Introduction

Concurrent chemoradiotherapy (CCRT) is a standard treatment for patients with locoregionally advanced uterine cervical cancer [1]. However, some Japanese physicians remain cautious about employing CCRT as a standard treatment, for 2 reasons. The first concerns the feasibility of using the standard chemotherapy of weekly 40 mg/m^2 cisplatin concurrently with radiotherapy. There have been several reports that Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 cisplatin may not be feasible for Japanese patients [2, 3]. The second is that there are limited data on CCRT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) [4, 5]. In addition, total radiation doses to the primary tumor seem to be extremely low compared with doses for definitive radiotherapy or CCRT in the United States [4–7]. A large amount of data concerning excellent outcomes and toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data were limited [8]. Therefore, the 2007 Japanese treatment guidelines for uterine cervical cancer recommended a B grade for CCRT [9]. We undertook a prospective study (JGOG1066) to evaluate toxicities and outcomes in patients treated with CCRT using the standard dose/schedule of cisplatin and the standard Japanese radiotherapy dose schedules for HDR-ICBT.

For scientifically valid CCRT clinical trial results, it is essential to develop an adequate protocol and assure compliance with the radiotherapy protocol. In developing the JGOG1066 protocol, several Japanese radiation oncology experts on cervical cancer undertook extensive deliberations on radiotherapy methods. In addition, effective quality assurance (QA) for radiotherapy was also discussed. In this paper, we describe the process for QA and present results of independent case reviews (ICRs) from the CCRT study.

Patients and methods

Summary of the JGOG1066

The Japanese Gynecologic Oncology Group (JGOG) conducted a phase II trial (JGOG1066) to evaluate the feasibility, toxicity and efficacy of CCRT using the standard global schedule for cisplatin (40 mg/m^2 weekly, 5 courses) and standard Japanese dose schedules for HDR-ICBT. Table 1 summarizes the trial, listing the criteria for patient eligibility, the endpoints, and treatments.

Protocol development

Radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with expertise in the treatment of cervical cancer. A nationwide questionnaire on radiotherapy methods including treatment schedules, delivery of an external beam radiotherapy (EBRT) boost to lymph nodes and the parametria, and bladder/rectum dose calculations (ICRU38) was first distributed to radiation oncologists. Treatment schedule queries included total and fractional doses of whole-pelvis EBRT (with/without midline block) and also total and fractional doses of HDR-ICBT. In developing protocols for radiotherapy methods, data from the questionnaire and from previous published reports were extensively discussed, and a consensus was reached.

To determine location of point A, a rule was established based on the topographical relationships between tandem and ovoid. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) was selected as the geographic origin of point A. In cases where the external os was located caudally to the cranial ovoid

Y. Hirashima
Department of Gynecology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

Y. Aoki
Department of Obstetrics and Gynecology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan

K. Umayahara · K. Takizawa
Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan

Table 1 Summary of JGOG1066

Eligible patients

1. FIGO stage III/IVA uterine cervical cancer
2. Squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma
3. ECOG performance status 0–1
4. Age 20–70 years
5. No para-aortic lymphadenopathy (≥10 mm assessed by CT)
6. No prior treatment
7. Adequate organ (bone marrow, hepatic, renal, heart) functions
8. Written informed consent

Endpoints

Primary: 2-year progression-free survival rate

Secondary: treatment completion rate, toxicity rates (acute and late), complete response rate, 2-year survival rate, 2-year pelvic progression-free rate, 2-year distant metastases-free rate

Planned sample size and accrual duration:

70 within 2 years

Treatment

Concurrent chemoradiotherapy (CCRT)

Chemotherapy

Cisplatin 40 mg/m^2, weekly, 5 courses

Radiotherapy

External beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT)

Radiotherapy schedules

WP	WP + MB	HDR-ICBT[a]	BED (WP + HDR-ICBT)[a]
30 Gy/15f	20 Gy/10f	24 Gy/4f	74.5Gy$_{10}$
30.6 Gy/17f	19.8 Gy/11f	24 Gy/4f	74.4Gy$_{10}$
40 Gy/20f	10 Gy/5f	18 Gy/3f	76.8Gy$_{10}$
41.4 Gy/23f	9 Gy/5f	18 Gy/3f	77.8Gy$_{10}$

WP whole pelvic radiotherapy, *MB* midline block, *BED* biologically effective dose, *f* fraction

[a] Prescribed at point A

surface (i.e. patients with roomy vaginal vaults), a coordinate at the vaginal vault was selected as the origin of the vertical level with the point A. The concept behind the latter definition is essentially the same as that of point H proposed by the American Brachytherapy Society (ABS) [6]. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules have almost biologically equivalent doses, the treating radiation oncologist was allowed to apply one of the schedules at their discretion. The protocol stated that enlarged pelvic node(s) (greater than 10 mm in the shortest diameter) visualized by pretreatment computed tomography (CT)/magnetic resonance imaging (MRI), and palpable nodular parametrium(s) fixed to the wall(s) should received an EBRT boost, with a total dose of 6–10 Gy/3–5 fractions.

To maintain radiotherapy quality, methods for QA were also examined. A credentialing process for participating institutions and independent case reviews (ICRs) of all treated patients were adopted for the QA. A description of the QA process was included in the protocol.

Credentialing

For institutional participation in this study, credentialing was required. The participating institutions had to meet the following 3 criteria:

1. Institution was certified by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) with JASTRO-certified radiation oncologist(s).
2. All HDR-ICBT procedures (i.e., applicator insertions, calculations, and evaluations) were carried out by JASTRO-certified radiation oncologist(s) or their colleagues.
3. At least 10 cervical cancer cases per year were treated by definitive radiotherapy using HDR-ICBT.

Meeting the first requirement indicated that the institution had a specified accuracy of external beam radiation dose delivery, since JASTRO-certified institutions must regularly undertake output measurements and calibrations of their linear accelerators. The second and third

requirements aid in ensuring that the HDR-ICBT procedure is performed with a reliable degree of skill.

Credentialing was undertaken by the JGOG radiotherapy committee. First, the committee identified JASTRO-certified institutions from 237 JGOG member institutions. Next, the committee asked those institutions if they would like to participate in the study. Institutions responding "yes" were subsequently requested to submit applications providing the following information: name of radiation oncologist(s) performing HDR-ICBT, name of radiologic technician(s) and physicist(s) responsible for HDR-ICBT, number of cervical cancer patients treated by definitive radiotherapy with HDR-ICBT per year, models and manufacturers of the HDR-ICBT machine and planning computer, source strength verification at the time of source replacement, and verification of source positioning in the catheter. With this information, the committee arrived at a consensus on whether or not an institution could participate in the study.

ICR summary

Participating institutions were requested to submit radiotherapy data for all treated patients. Table 2 lists the submitted items. Radiotherapy charts describing daily treatment records and treatment parameters were submitted as hard copies. Other graphical data (including simulation, digitally reconstructed radiography) and figures (including dose distributions) were submitted in digital formats on CD-ROMS. The radiotherapy committee performed ICRs on 18 QA items according to predefined evaluation criteria (Table 3). The QA assessment was classed as per protocol, deviation, and violation. QA evaluation criteria for ICRs were not included in the protocol description, but prepared separately.

Preliminary evaluations were performed by the study chair (T.T.). The preliminary evaluations were reviewed and approved by other JGOG radiotherapy committee members at the time of the QA meetings. The QA meetings were held twice (April 24, 2009, and May 7, 2010).

Table 2 Data submitted for ICR

External beam radiotherapy
Treatment charts (beam energy, SAD, gantry angle, field size, MU, plan summary sheets from RTPS, and daily treatment record)
Simulation films or DRRs
Verification portal films or EPIDs
Isodose distributions (central axis plane)
HDR-ICBT
Treatment charts for all sessions (activity, dwell times, dwell positions, and point doses)
AP and lateral orthogonal films or images for all sessions
AP and lateral isodose distributions for all sessions

ICR individual case review, *SAD* source-axis distance, *MU* monitor unit, *RTPS* radiotherapy treatment planning system, *DRR* digitally reconstructed radiographs, *EPID* electronic portal imaging devices, *HDR-ICBT* high dose-rate intracavitary brachytherapy, *AP* anterioposterior

Results

From March 2008 to January 2009, 72 patients from 25 institutions were enrolled. One patient who did not meet the eligibility requirements and 2 patients who stopped protocol treatment because of toxicities were excluded, leaving 69 patients who were considered eligible for the ICRs. Table 4 summarizes the ICR results. In 24 patients (35%), there were no deviations of any of the 18 ICR items. There were also no deviations seen in 5 of the 18 items (i.e., QA-1, -2, -3, -4, -8) in any of the 69 patients evaluated. Deviations were seen in 45 cases, and violations were observed in 4 cases. Table 5 lists the number of cases and number of ICR items assessed with a deviation or violation. Deviations were observed most frequently for QA-7, which evaluated the appropriateness of delivering an EBRT boost.

Details of QA evaluations

QA-1 EBRT beam energy: No deviations were seen. Beam energies included the following: 6 MV in 1 patient, 10 MV in 40 patients, 15 MV in 14 patients, 18 MV in 12 patients, and 20 MV in 2 patients.

QA-2 EBRT method: No deviations were seen. There were 28 patients treated with anteroposterior–posteroanterior (AP–PA) ports, and the remaining 41 patients were treated with the four-field box technique.

QA-3 Daily EBRT dose fraction: No deviations were seen. In 40 patients, 1.8 Gy was used, and in 29 patients, 2 Gy was used.

QA-4 Total EBRT dose of the whole pelvis (WP) with/without midline block (MB): No deviations from the protocol description were seen.

QA-5 MB set-up timing: One patient whose MB was set at 32 Gy received 24 Gy/4 fractions of HDR-ICBT; this was judged as a deviation. The remaining patients were all evaluated as per protocol. The MB was set at 30 Gy in 11 patients, 30.6 Gy in 33 patients, 40 Gy in 15 patients, and 41.4 Gy in 7 patients. There were 2 patients who

Table 3 Radiotherapy quality assurance items and criteria for ICR

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	≥6MV	<6MV or cobalt	–
QA-2: EBRT methods	AP–PA or 4-field box	Other methods	All ports not delivered each day
QA-3: EBRT daily fraction dose (prescribed)	1.8 or 2 Gy and 5 fractions/week	Other fraction dose and 5 fractions/week	4 fractions/week
QA-4: EBRT total dose (prescribed)	<±5%	5–10%	>±10%
QA-5: MB set-up timing	1. 30/30.6/40/41.4 Gy	1. 30–41.4 Gy, but not 30/30.6/40/41.4 Gy	Before 30 Gy
	2. after 41.4 Gy with certain clinical validity	2. after 41.4 Gy without certain clinical validity	
QA-6: EBRT treatment portals	WP with proper coverage	WP with improper coverage	Extended fields (covering para-aortic nodes)
QA-7: EBRT boost	Performed properly/not applicable	Not performed even applicable/performed but improperly	–
QA-8: EBRT dose homogeneity within PTV[a]	95–107%	<95 or >107%	–
QA-9: Divergence between simulation and verification	≤5 mm and no difference in shape	≥6 mm or different shape	No verification
QA-10: Timing of the first HDR-ICBT	After 30–41.4 Gy and within 7 days from MB insertion	After 30–41.4 Gy but over 7 days from MB insertion	Before 30 Gy
QA-11: EBRT and HDR-ICBT on same day	No	–	Yes
QA-12: HDR-ICBT planning for each fraction	Yes	–	No
QA-13: HDR-ICBT fraction dose (at point A, prescribed)	6 Gy and once a week	Other than 6 Gy (<7.5 Gy) or ≥twice a week	≥7.5 Gy
QA-14: HDR-ICBT total dose (at point A, prescribed)	18 or 24 Gy	Other than 18 or 24 Gy	≥30 Gy
QA-15: Determination of point A	As stated in protocol	Not as stated in protocol	–
QA-16: Dose calculation at OARs (rectum, bladder; ICRU 38)	Yes	No	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed, BED at point A)	As stated in protocol (74–78 Gy_{10})	Not as stated in protocol but 70–80 Gy_{10}	<70 Gy_{10} or >80 Gy_{10}
QA-18: Overall treatment time	≤8 weeks	8–10 weeks	>10 weeks

ICR individual case review, *EBRT* external beam radiotherapy, *AP–PA* anteroposterior–posterioanterior, *MB* midline block, *WP* whole pelvis, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk, *BED* biological effective dose

[a] At level of field isocenter

received 50 Gy of whole-pelvis EBRT without MB, in whom the treating radiation oncologists thought that adequate shrinkage of the primary tumor had not been achieved for effective ICBT. This situation had been described as "clinically appropriate" in the protocol, and was judged per protocol.

QA-6 EBRT treatment portals: There were 6 patients with deviations. These were all from a single institution, and planning was based on clinical target volume (CTV) contouring on CT images.

QA-7 EBRT boost: In 32 patients, the EBRT boost was not applied appropriately as stated in the protocol. These were judged as deviations.

QA-8 EBRT dose homogeneity within planning target volume (PTV): No deviations were seen.

QA-9 Geometrical divergence between simulation and verification: There were 3 patients from a single institution for whom a geometrical divergence ≥5 mm was seen. These were judged as deviations.

QA-10 Timing of the first HDR-ICBT. There were 2 patients whose first HDR-ICBT was delayed for ≥7 days, which was judged as a deviation. There