Real-time tumor-tracking irradiation techniques

A real-time tumor-tracking irradiation technique is an RMM technique corresponding to either (i) or (ii) below, performed under unforced breathing, and is defined as a technique that meets the requirements for RMMs specified in ***RMMs***. It is acceptable to control respiration (e.g. improvement of the regularity of respiration, and shortening of the length of the respiratory tumor motion), aiming to improve the tracking accuracy and irradiation efficiency if necessary.

(i) *A technique to perform the irradiation by analyzing the relationship between respiratory movement and tumor, and changing the irradiated field in accordance with the respiratory movement.* When a model which predicts the 3D position of a tumor with external breathing signals or other indicators is used, the model for the prediction must be created directly before the start of irradiation and updated during the treatment as required. It is necessary to measure external breathing signals or other indicators several times per second, and to verify that a tumor is included in the irradiated area based on the model of the prediction. If no prediction model is used, tumor positions must be verified three-dimensionally several times per second during the irradiation.

(ii) *A technique to perform the irradiation onto a target while it passes through a specified position, by observing a tumor or a marker in the vicinity of the tumor using a fluoroscope during the irradiation.* When using a fluoroscope during the irradiation, it is necessary to verify that a tumor is included in the irradiated area while determining the tumor position three-dimensionally several times per second.

Examples of measures that may be considered with RMM

The following six methods are described as examples of measures to include with RMMs in the 2008 Guidelines for Radiotherapy Planning [5]:

(i) inhalation of oxygen;
(ii) abdominal compression: a method to secure a part of the abdomen by a band or shell, a method that uses an abdominal compression board, and others;
(iii) learning of regular respiratory patterns (the metronome method);
(iv) breath hold technique: active breathing control, self-respiratory cessation in deep inspiration, self-respiratory breath-monitoring measured at two thoraco-abdominal points;
(v) gating with respiration;
(vi) real-time tumor-tracking: pursuing irradiation and intercepting irradiation.

If a technique satisfies the requirements listed in the definition of RMMs, it may be accepted for inclusion as an RMM. However, it is generally difficult to meet the requirements if (i) inhalation of oxygen, or (iii) learning of regular respiratory patterns, is used alone.

Measure (vi) is regarded as a 'real-time tumor-tracking irradiation technique', and techniques to pursue and intercept correspond to ***Real-time tumor-tracking irradiation techniques*** (i) and (ii), respectively.

Examples of methods to establish and verify the length of respiratory-induced tumor motion

- X-ray fluoroscopy
- 4D computed tomography (CT)
- Ultrasonography
- Cine magnetic resonance imaging (MRI)

Examples of methods to verify that a tumor is included in the irradiated area

Immediately prior to the irradiation:

- CT integrated with the therapeutic apparatus (cone-beam CT, MVCT, and others)
- CT which is installed in the room where radiotherapy is performed
- Fluoroscopy that verifies at least two directions

During the irradiation:

- Cine electronic portal imaging device (EPID)
- X-ray fluoroscopy
- Model which predicts the 3D position of a tumor from external breathing signals and others

If satisfying the requirements listed in ***RMMs*** and ***Real-time tumor-tracking irradiation techniques***, other methods that are not specifically listed above may be utilized in RMM.

Diseases where the treatments described here may be applied

The treatments described here may be considered for the diseases listed below, but only when the length of the targeted respiratory tumor motion exceeds 10 mm.

External irradiation other than stereotactic radiotherapies:

- lung cancer, esophageal cancer, gastric cancer, liver cancer, carcinomas of the biliary tract, pancreatic cancer, renal cancer, or adrenal cancer.

Stereotactic radiotherapies:

- primary lung cancer and primary hepatic cancer which show no metastatic lesions and where the primary focus is 5 cm or less in diameter;
- metastatic lung cancer or metastatic hepatic cancer with ≤ 3 focuses, which are 5 cm or less in diameter, and with no focuses in other organs.

Note that although arteriovenous malformation of the spinal cord is treated with stereotactic radiotherapies, it has no respiratory motion and RMM considerations do not apply.

INSTITUTIONAL STANDARDS RELATED TO THE IMPLEMENTATION OF RMMS

For RMM to be adopted, it must meet the following institutional standards.

The institutional standards relate to the requirements for personnel, instruments, and the keeping of records as detailed below.

Requirements for personnel

The following staff must be available when performing the external radiotherapy involved in RMM:

(i) one or more full-time radiation oncologists;
(ii) one or more full-time radiological technologists (with more than five years' experience with radiotherapy required);
(iii) one or more medical physicists, radiotherapy quality managers or radiological technologists in charge of QA/QC.

Adoption of stereotactic radiotherapies as an RMM (other than real-time tumor-tracking irradiation) technique has the same staff requirements as external radiotherapy.

The following staff must be available when performing stereotactic radiotherapy (with real-time tumor-tracking irradiation technique) in RMM:

(i) two or more full-time radiation oncologists (one must have more than five years' experience with radiotherapy);
(ii) one or more full-time radiological technologists (with more than five years' experience with radiotherapy);
(iii) one or more medical physicists, radiotherapy quality managers or radiological technologists in charge of QA/QC.

In the Guidelines for improving collaboration among central medical facilities for cancer treatments (Document number 0301001, announced on March 1 2008, and partially revised on March 29 2011, by the Director of Health Service Bureau, Ministry of Health, Labour and Welfare), the terms, 'exclusively in charge of' and 'exclusively engaged in', are defined as follows:

'Exclusively in charge of' means that the person is exclusively in charge of the said therapy. In this case, if the person is exclusively in charge of the therapy, this person may also be in charge of other duties. However, the person must be in charge of the said therapy for more than 50% of the working hours.

'Exclusively engaged in' means that the person is exclusively engaged in the said therapy on the day when the said therapy is performed. In this case, the person must be engaged in the said therapy for more than 80% of the working hours.

Staff allocation scheme recommended for RMM

The present guidelines recommend the establishment of the following staff allocation scheme to ensure safety in the implementation of RMM. Note that the personnel in charge should not be assigned additional duties.

Radiation oncologists

It is recommended that radiation oncologists must be exclusively engaged in the therapy and not in charge of the overall treatment. It is also recommended that the radiation oncologists have more than five years' experience with radiotherapy, and be Board-certified radiation oncologists, certified medical specialists of radiotherapy, acknowledged by both the Japanese Society for Therapeutic Radiology and Oncology, and the Japan Radiological Society.

Radiological technologists

Radiological technologists must have more than five years' experience with radiotherapy, and it is recommended that they be qualified radiological technologists certified by The Japan Professional Accreditation Board for Radiotherapy Technologists. It is also recommended that radiological technologists be exclusively engaged in the therapy and not exclusively in charge of the overall treatment.

Medical physicists, radiotherapy quality managers or radiological technologists in charge of QA/QC

For the safety control of medical instruments, it is recommended that one (or more) full-time radiological technologist(s) and/or radiotherapy quality manager(s), and one or more full-time medical physicist(s) exclusively in charge of

the quality control of the radiotherapy instruments be assigned to the staff for RMM, and as well there must be a radiological technologist directly engaged in the irradiation operation, together with a physicist.

The former must be (a) qualified radiological technologist (s) specializing in radiotherapy and certified by The Japan Professional Accreditation Board for Radiotherapy Technologists, or (a) qualified radiotherapy quality manager (s) certified by the Japanese Organization of Radiotherapy Quality Management. The medical physicist(s) described here must be a medical physicist(s) certified by the Japanese Board of Medical Physics (JBMP). It is recommended that the two kinds of professionals described here must be exclusively engaged in radiotherapy and not in charge of the overall treatment. Further, they must have more than five years' experience in quality control of radiotherapy instruments, verification of irradiation plans, supplemental work related to irradiation plans, and other matters.

Radiation oncology nurses

It is necessary to ensure patient understanding and cooperation in RMM before it is implemented, and it is indispensable for medical staff to fully understand the respiratory condition while patients are receiving treatment. Although 'nurses' is a professional category that is not clearly specified in the document for medical treatment fees, these Guidelines recommend that nurses be assigned to the roles detailed here. These nurses should be exclusively in charge of the radiotherapy as it is essential to closely observe patient conditions from the time the treatment plans are established throughout the treatment.

Requirements for instruments for the treatment

Instruments meeting the following requirements must be installed in the room where the radiotherapy is performed:

(i) instruments to accommodate respiratory motion when the length of respiratory tumor motion exceeds 10 mm, and to compensate for the expansion of irradiated areas smaller than 5 mm;
(ii) instruments to verify and record that the tumor is included in the irradiated area immediately prior to and during the irradiation in each irradiation event.

Although not specified in the section detailing institutional standards, it is also necessary to provide instruments that can verify lengths of respiratory motion exceeding 10 mm when RMM is not performed. Such instruments are not necessarily installed in the room where the radiotherapy is performed.

Requirements for keeping records

Medical institutions authorized to treat patients with health insurance coverage must keep and store records related to RMM, and also records related to quality control of activities. These records must be available to the public.

Records of activities

The following particulars must be verified and recorded in medical and irradiation records, as the data contained here may show therapeutic gains or adverse events.

Considerations when making treatment plans:

(i) cases where the length of respiratory motion exceeds 10 mm without RMM. (Recording of numerical data for each of the three-dimensional directions is recommended.)
(ii) cases where the expansion of the irradiated area has been reduced to 5 mm or less in each of the three-dimensional directions.

Immediately prior to and during the irradiation:

(iii) cases where a tumor is included in the irradiated area based on verification imaging or a prediction model.

Quality control records

A quality control program for RMM must be developed and adhered to as a regular procedure. It is recommended that staff exclusively in charge of quality control report the results to other professionals concerned, and maintain the data in a manner to enable access as necessary. It is also recommended that the quality control program include the following data as related to the RMM procedures used in the particular institution:

(i) data related to quality control of CT for treatment plans when using a respiratory monitoring system;
(ii) data related to calibration and accuracy of the position of tumors (or marker in the body which represents tumor positions), or external breathing signals identified by the treatment system, including a respiratory monitoring system;
(iii) data related to output characteristics of treatment beams and the period of time from sensing the respiratory phase to the actual irradiation when using a respiratory monitoring system;
(iv) data related to dose verification in the RMM;
(v) data related to radiation exposure required for the RMM;
(vi) data related to the quality control of devices verifying the position of irradiation;
(vii) data related to interlocking with the full treatment system, including the respiratory monitoring system.

Note that using a moving phantom that can reproduce respiratory movement is recommended for quality control of the RMM.

Treatment plans for RMM

When performing RMM, a treatment plan must be established assuming the following uncertainties:

(i) changes in the tumor form due to respiration;
(ii) errors between the predicted and actual tumor positions;
(iii) the length of time from sensing the respiratory phase to the actual initiation of irradiation.

In general, the area to be irradiated is determined by adding a margin (about 5 mm) to the PTV. However, this should not be done for compensating the respiratory motion because it is for ensuring the dose at the PTV periphery.

Functions of specialists participating in RMMS

The functions of the specialists applying RMM, detailed in these Guidelines, are as follows:

Radiation oncologists

The functions of the radiation oncologists are:

(i) to determine if RMM is appropriate for a patient;
(ii) to explain the benefits and risks of RMM to the patient, and obtain consent to conduct the treatment;
(iii) to conduct discussions among the specialists involved, and determine specifics of how RMM is to be conducted;
(iv) to provide patient information required for performing RMM to other specialists involved, prior to carrying out the treatment planning (including CT scan for treatment plans);
(v) to establish appropriate guidelines for 'the expansion of area of irradiation required to compensate for respiratory motion', based on the clinical data, particulars of the equipment characteristics in the particular institution, and patient conditions;
(vi) to verify the records that a tumor has been included in the irradiated area immediately prior to and during the irradiation procedures. If the tumor is not included, discuss this with other specialists and determine whether it is appropriate to modify the treatment plans or to change the irradiation technique to a usual method without respiratory motion management.
(vii) to supervise RMM to ensure that it is carried out appropriately;
(viii) to make clinical evaluations of the appropriateness of the radiation exposure when radiation exposure cannot be avoided in carrying out RMM; and
(ix) to discuss quality control related to RMM with the specialists involved and verify the results.

Radiological technologists

The functions of the radiological technologists are:

(i) to perform a CT scan, considering the fluoroscopy and respiratory-induced motion, in order to verify and record the length of respiratory-induced tumor motion. Perform a CT scan for the treatment plan that takes account of RMM to be employed. As necessary, train the patient in breathing and other particulars in advance of conducting the treatment.
(ii) to ensure a thorough understanding of the use of the instruments and devices to fix the patient position described in the ***Requirements for instruments for the treatment*** above;
(iii) to ensure availability of information necessary to verify that the tumor is included in the irradiated area immediately prior to and during the irradiation, and record the results;
(iv) to suspend irradiation if the tumor is not included in the irradiated area during the irradiation. Promptly report this to the other personnel and specialists involved, discuss this with the other specialists, and determine whether it is appropriate to modify the treatment plans or to change the irradiation technique to a usual method without RMM.
(v) to monitor the patient during the irradiation, and be ready to stop the irradiation if required;
(vi) in case of problems with the instruments described in the ***Requirements for instruments for the treatment***, report this to the staff in charge of quality control. Work, together with the other staff, to restore the functioning of the instruments, and ensure safety.

Medical physicists, radiotherapy quality managers or radiological technologists in charge of QA/QC

The functions of the medical physicists, radiotherapy quality managers or radiological technologists in charge of QA/QC are:

(i) to draw up and carry out a quality control plan related to RMM; also, to evaluate the results

and be in charge of the recordings and records of the operation.

(ii) in case of problems with the instruments described in the ***Requirements for instruments for the treatment***, take the initiative to restore the functioning of the instruments and confirm safety;

(iii) to suggest optimal methods of carrying out RMM by taking account of the physical characteristics of the treatment beams and the total treatment time;

(iv) to determine whether the irradiated area has become smaller than without RMM;

(v) to verify that the setting of the margins and irradiated area are appropriate for the employed RMM. When determined inappropriate, develop alternative treatment plans together with the radiation oncologists involved.

(vi) to observe the confirmation of the position to be irradiated immediately prior to and during the irradiation, and to discuss the results with the other staff involved; to make proposals for necessary changes in the treatment plans or using the regular planned irradiation if the tumor is not included in the irradiated area.

(vii) in the case of radiation exposure to areas other than that planned for the treatment beams in carrying out RMM, to measure radiation exposure and report it to the other staff and specialists involved.

Radiation oncology nurses

The functions of the radiation oncology nurses are:

(i) to conduct patient orientation prior to the treatment so that the patient will know what the treatment is going to be like, and thus to assist patient understanding of RMM;

(ii) to consider ways to provide interventions to the patient, while regularly assessing the patient understanding of the treatment and the ability of the patient for self-care;

(iii) in the case that a patient experiences acute pain, have in place appropriate arrangements for preventive internal analgesic medications and the timing of their administration;

(iv) for patients who are subject to stress-induced rapid breathing, carefully consider the method of movement of the patients to the treatment room, and provide necessary assistance to ensure that the patient is comfortable during the treatment;

(v) for patients prone to high levels of unease and stress, attend to the patient and create an atmosphere enabling the patients to relax and be encouraged;

(vi) for patients who may pose risks of deterioration in respiration due to having to remain in an unchanging position for a long period of time, monitor oxygen saturation.

CONCLUSIONS

These Guidelines have been developed as a general introduction aiming at providing safe and appropriate RMM. New techniques for RMM are being developed and these Guidelines may be revised as necessary. Therefore, it is necessary to pay close attention to published reports in Japan and other countries to endeavor to provide optimally appropriate RMM.

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The draft of these Guidelines was peer-reviewed by third parties, which consisted of the Quality Assurance Committee, the Guideline Committee, the Health Insurance Committee in Japanese Society for Therapeutic Radiology and Oncology, the Quality Assurance/Quality Control Committee of the Japan Society of Medical Physics, and the Subcommittee for Radiotherapy in the Japanese Society of Radiological Technology.

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CONFLICT OF INTEREST

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Clinical Investigation: Gynecologic Cancer

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

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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

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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. © 2012 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

Parameters	No. of patients (%) 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 (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
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.

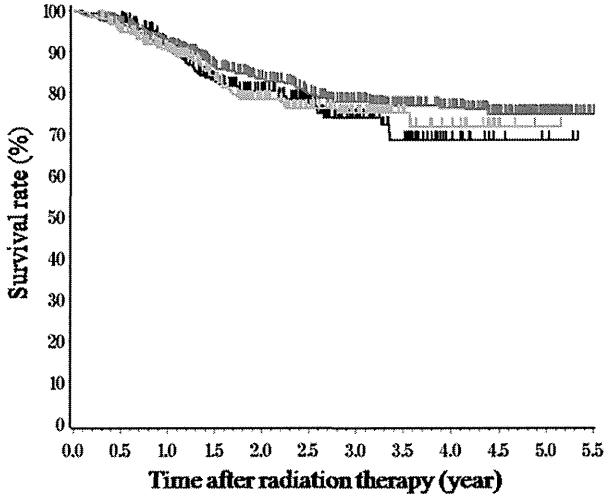

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

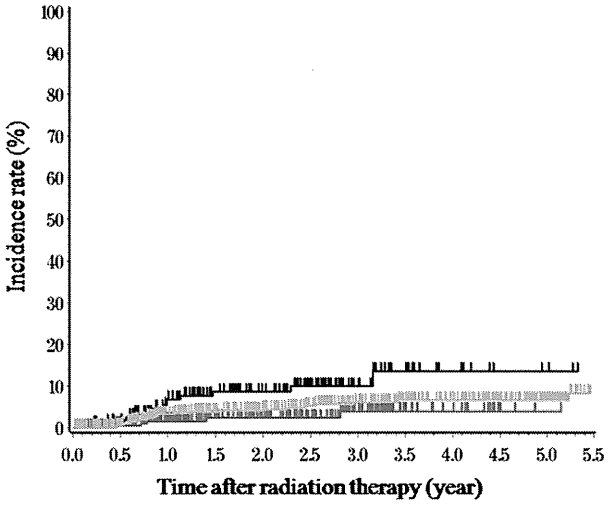

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

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.

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CLINICAL INVESTIGATION **Gynecologic Cancer**

INTERNATIONAL BRACHYTHERAPY PRACTICE PATTERNS: A SURVEY OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

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Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/New Zealand (ANZ), Europe (E), and North America (NAm).

Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.

Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) ($p = 0.02$). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; $p = 0.02$ for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan ($p = 0.0002$).

Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials. © **2012 Elsevier Inc.**

Brachytherapy, Cervical cancer, Radiation dose.

INTRODUCTION

Globally, cervical cancer represents the most common gynecologic malignancy (1). Patients with locally advanced cervical cancer (Stage IB2–IVA) require treatment with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (2). The recommended cumulative dose of EBRT and brachytherapy to cure locally advanced disease

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ranges from 80 to 90 Gy recorded at point A using low-dose-rate (LDR) brachytherapy (2).

Over the past 20 years, high-dose-rate (HDR) brachytherapy has increased and replaced LDR in many practices (3). The Patterns of Care for cervical cancer radiation practice in the United States reported a 16% HDR utilization rate in 1999 (4), whereas 85% of surveyed physician members of the American Brachytherapy Society (ABS) reported having HDR at their institution in 2007 (3). Overall, randomized studies indicate that outcomes with HDR resemble those with LDR, though many issues exist regarding the methodology of randomization and the follow-up duration across the studies (5). However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of computed tomography (CT) or magnetic resonance imaging (MRI) to determine doses to the tumor and the organs at risk (6).

The biologic equivalent dose formulas allow calculation of the brachytherapy dose (7, 8). However, these formulas require an assumption that the α/β ratio for tumor is 10, which may be an underestimation for squamous cell carcinoma. Furthermore, concerns regarding the validity of the linear quadratic model exist for very low or very high doses per fraction (9). Publication of standard fractionation regimens for HDR cervical cancer brachytherapy with point A–based standard loading (10, 11) led to widespread adoption in the United States of the regimen 6 Gy for five fractions over approximately 2.5 weeks. Preliminary results demonstrate a 2-year Grades 3 and 4 bowel toxicity rate of 11% with this HDR regimen (12). By contrast, with 2-year follow-up, only three (5%) Grade 3 or greater gastrointestinal complications occurred in a group of 65 patients treated with 6 Gy for five fractions in one report (13). It remains unknown whether 6 Gy for five fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR brachytherapy.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups to move the development of oncologic clinical trials forward in a highly constructive and cost-effective manner. Randomized trials with international participation will accrue cervical cancer patients rapidly and result in advances on a global stage. To determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. The goal is to clarify which regimen would be acceptable for future international collaborative clinical trials.

METHODS AND MATERIALS

The GCIG represents an international association of member cooperative groups conducting large clinical trials for gynecologic malignancies. Since its inception in 1997, 18 cooperative groups have joined, including the AGO-Austria (Austria), AGO-OVAR (Germany), ACRIN (USA), ANZOG (Australia, New Zealand), DGOG (the Netherlands), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRI (Great Britain), NCIC (Canada), NSGO (Scandinavia), RTOG (USA), SGCTC (Scotland), and SWOG (USA).

A 32-question survey was designed to address questions regarding standard practice patterns for locally advanced cervical cancer management, such as routine doses of external beam and the use of concurrent chemotherapy, and also to determine baseline brachytherapy practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix EI available online at at www.redjournal.org). An e-mail providing background information, the purpose of the survey, and a link to a web page for easy retrieval of the survey was sent electronically to the chair of each GCIG member cooperative group in December 2008. Each cooperative group chair could choose to forward the email to six radiation oncology members from separate representative centers that had a large volume of cervical cancer cases. Respondents could complete only one survey on a computer, and entered their names and e-mail addresses to avoid duplicate submissions. The survey website closed in May 2009. Appendix E1 (available online at at www.redjournal.org) lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. For respondents that used a midline block, the total dose to the nodes and the dose to the cervix were summed separately. The EBRT and brachytherapy EQD2 doses were calculated at point A for patients with Stage IB–IIA and those with Stage IIB-IVA disease; then the average was taken for a cumulative sum for all stages. Analysis of reported HDR fractionation regimens was divided by country and by region, including Asia (Japan/Korea); Australia/New Zealand; Europe (Austria, Denmark, England, Finland, Germany, Italy, Ireland, the Netherlands, Scotland, Spain); and North America (USA, Canada). Quartiles of dose were evaluated to determine whether any particular region or country grouped into the highest or lowest dose ranges. The *t*-test statistic was performed to determine whether any significant differences in dose existed by region.

RESULTS

Respondent characteristics

A total of 16 cooperative groups gave member responses to this survey. Of 74 respondents, two were excluded: one non-GCIG member and one GCIG member who did not answer questions regarding brachytherapy, yielding a final study population of 72 respondents. Cooperation was received from the AGO-Austria (n = 3), ABO-Germany (n = 2), ACRIN (n = 1), ANZGOG (n = 6), DGOG (n = 6), EORTC (n = 5), GEICO (n = 1), GOG (n = 5), JGOG (n = 6), KGOG (n = 4), MANGO (n = 3), MITO (n = 2), MRC/NCRI (n = 9), NCIC (n = 10), NSGO (n = 3), and the RTOG (n = 6). Regions of the world represented were Japan/Korea (n = 10), Australia/New Zealand (n = 6), Europe (n = 34), and North America (n = 22).

Of the 72 respondents, 63 (88%) practice radiation oncology; 8 (11%), both medical and radiation oncology; and one (1%), gynecologic oncology. Regarding the average number of cervical cancer patients treated per year, 7 (10%) treat 1 to 9, 18 (25%) treat 10 to 19, 11 (15%) treat 20 to 29, 9 (13%) treat 30 to 39, 6 (8%) treat 40 to 49, 10 (14%) treat 50 to 59, 6 (8%) treat 60 to 69, 4 (6%) treat 70 to 79, and 1 (1%) treats more than 140.

External-beam radiation to the cervix

Physicians were queried regarding the standard EBRT dose prescribed for treating cervical cancer. For those who reported administering a parametrial boost dose, the parametrial doses were excluded from the EBRT cumulative cervical dose calculation, since the goal of a midline block is to avoid significant radiation to the cervix during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose was 44.2 Gy (range, 19.8–50.4) for Stage IB–IIA patients and 47.2 Gy (range, 30.6–54) for Stage IIB–IVA patients. The average cervical dose for the Japanese respondents (not including the parametrial boost dose) was 23.3 Gy (range, 19.8–30) for Stage IB-IIA patients and 36.7 Gy (range, 30.9–40) for Stage IIB–IVA patients. All Japanese respondents commented that after insertion of a midline block, the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after insertion of the midline block). By contrast, all other countries reported a mean EBRT dose of 46.11 Gy (range, 40–50.4) for Stage IB–IIA patients and 48.2 Gy (range, 40–54) for Stage IIB–IVA patients. The most commonly added parametrial boost dose is 5.4 Gy after 45 Gy to the entire pelvis. For Stage IB–IIA patients, the most common EBRT doses are 45 Gy (n = 41, 57%) and 50.4 Gy (n = 15, 21%). For Stage IIB–IVA, the most common EBRT doses are 45 Gy (n = 26, 36%), 50.4 Gy (n = 27, 38%), and 54 Gy (n = 5, 7%).

All respondents prescribe concurrent chemotherapy with EBRT. In addition, 4% (three respondents) consider giving neoadjuvant chemotherapy before concurrent chemoradiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-flourouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

Brachytherapy

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) had LDR, and 8 (11%) have pulse-dose-rate. Chemotherapy is given on the same day as an HDR fraction by four respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by three respondents (4%). A total of 38% of respondents might hospitalize patients overnight for HDR treatment. For those using LDR, an equal number of respondents use on average one or two fractions, with a per-fraction dose ranging from 10 to 40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, pulse-dose-rate, and LDR, with 54% using this applicator for more than 75% of their cases annually. The tandem and ring applicator is used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, 97% of respondents' patients receive anesthesia, consisting of general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%). Ultrasound is used for assistance with applicator insertion by 62% of respondents; 24% use ultrasound less than 10% of the time, 12% use it for 10–25% of cases, 7% use it for 26–50% of cases, 1% use it for 51–75% of cases, and 18% use it for more than 75% of their cases.

With regard to imaging the brachytherapy applicator after insertion, 17 centers (24%) reported that they use plain x-ray films, either alone or in combination with MRI and/or CT. By contrast, CT is the most commonly used imaging modality (n = 41, 57%); 27 respondents use CT for every fraction, and 14 use CT for the first fraction only. MRI is used by 18 centers (25%), of which eight use MRI for every fraction and 10 for the first fraction only; of these 10, eight acquire a CT scan for every fraction. In terms of prescribing to the cervix, 56 (78%) prescribe to point A, 8 (11%) follow the GEC-ESTRO guidelines (14, 15) alone, 15 (21%) follow the GEC-ESTRO and report dose to point A, 4 (6%) follow the ABS guidelines alone, and 8 (11%) use both the ABS and point A.

The major HDR fractionation patterns are depicted in Fig. 1 and listed in the table. For Stage IB–IIA patients, the most common HDR fractionation pattern is 6 Gy for five fractions (n = 11, 15%), as it is for Stage IIB–IVA patients (n = 14, 19%). A total of 28 fractionation regimens are reported, of which 18 are used by only one institution. The most common fractionation regimen, 6 Gy for five fractions, is prescribed by centers in the United States, Canada, Australia, New Zealand, the United Kingdom, Spain, Italy, and Germany. The second most common regimen, 7 Gy for four fractions, is prescribed by centers in the United States, Australia, Austria, and the Netherlands. For HDR dose reporting, of the 68 respondents to this question, 32 (47%) calculate equivalent dose using the 2-Gy (EQD2) formula, whereas 31 (46%) use only the biologic equivalent dose formula, and five (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT plus brachytherapy EQD2 was 78.9 Gy (standard deviation [SD] 10.7) for Stage IB–IIA patients and 83.3 Gy (SD 11.2) for Stage IIB–IVA patients for all countries (p = 0.02 Stage IB–IIA vs. IIB–IVA). For all stages and all countries, the mean EBRT plus brachytherapy dose was 80.9 (SD 10.14). By region, the mean combined EQD2 for Australia/New Zealand was 81.18 (SD 4.96); for Europe, 83.35 (SD 10.75); for North America, 81.66 (SD 6.05); and for Asia, 71.2 Gy (SD 12.65; p = 0.02 for Asia vs. other regions). The mean EBRT plus brachytherapy dose for Japan was 62.73 (SD 6.7), and for Korea it was 83.9 (SD 6.86). Therefore, the only significant difference was between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, and 1 New Zealand) had EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) reported EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose was from a center that uses a fractionation regimen of 7 Gy for seven fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

The average ratio of brachytherapy dose to total sum (EBRT plus brachytherapy) dose was 0.45 (SD 0.08) for Stage IB–IIA and 0.44 (SD 0.08) for Stage IIB–IVA (p = NS). However, for Japanese respondents, the all-stages ratio

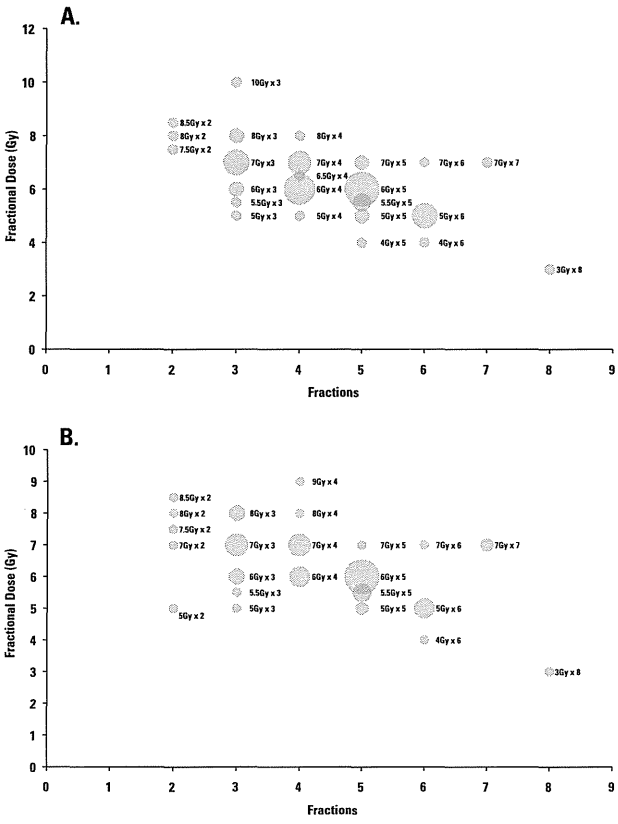

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages 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.

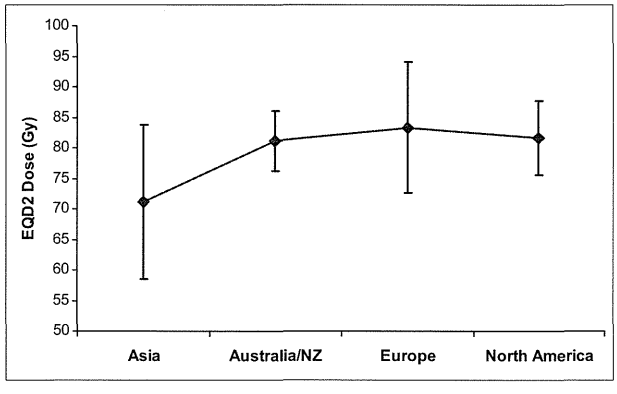

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

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.

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