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

Table 4 Radiotherapy ICR summary: JGOG1066

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	69	0	–
QA-2: EBRT method	69	0	0
QA-3: EBRT daily fraction dose (prescribed)	69	0	0
QA-4: EBRT total dose (prescribed)	69	0	0
QA-5: MB set-up timing	68	1	0
QA-6: EBRT treatment portals	63	6	0
QA-7: EBRT boosts	37	32	0
QA-8: EBRT dose homogeneity within PTV	69	0	–
QA-9: Divergence between simulation and verification	66	3	–
QA-10: Timing of the first HDR-ICBT	65	2	2
QA-11: EBRT and HDR-ICBT on same day	68	–	1
QA-12: HDR-ICBT planning for each fraction	68	–	1
QA-13: HDR-ICBT fraction dose (prescribed)	66	3	0
QA-14: HDR-ICBT total dose of (prescribed)	65	4	0
QA-15: Determination of point A	64	5	–
QA-16: Dose calculation of OARs (ICRU38)	66	3	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed)	67	2	0
QA-18: Overall treatment time	66	3	0

ICR individual case review, *EBRT* external beam radiotherapy, *MB* midline block, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk

were 2 patients who received their first HDR-ICBT before 30 Gy of EBRT had been administered, which was judged as a violation.

QA-11 Prohibition against same-day delivery of EBRT and HDR-ICBT: There was 1 patient who received both EBRT and HDR-ICBT on the same day, which was judged as a violation.

QA-12 HDR-ICBT planning for each fraction: The protocol stated that dose calculations should be performed for every HDR-ICBT session. There was 1 patient who received her second and third HDR-ICBT based on planning data from her first application. This was judged as a violation.

QA-13 HDR-ICBT fraction dose: There were 2 patients who received HDR-ICBT with an incorrectly prescribed point A dose, which was judged as a deviation. Another patient received HDR-ICBT using an inappropriate reference point instead of point A, which was also judged as a deviation.

QA-14 HDR-ICBT total dose: The 3 patients with QA-13 deviations and 1 patient who did not receive the last HDR-ICBT because of acute toxicity were judged as deviations.

QA-15 Determination of point A: There were 5 patients who received HDR-ICBT at an incorrectly defined point A. These were judged as deviations. One of those patients also had deviations for QA-13 and -14. In 4 of these patients, the external os was selected as the geometrical origin for point A instead of the vaginal vault level (which was the correct definition), although the external os was located caudally to the cranial ovoid applicator surface.

Table 5 Numbers of cases and quality assurance items with deviations or violations

Number of deviations	Number of cases[a]
0	24
1	36 (2)
2	6 (1)
3	0
4	1 (1)
5	1
6	0
7	1

[a] Parentheses include number of cases also having violations

QA-16 Organs at risk (OAR) dose calculation [10]: Bladder dose calculations were not performed in 3 patients, which were judged as deviations.

QA-17 Total EBRT and HDR-ICBT dose: Two of 3 patients who had deviations in QA-13 were also assessed with deviations for this.

QA-18 Overall treatment time (OTT): There were 3 deviations in OTT. The OTTs of these 3 patients were 56, 57, and 65 days. The longest OTT was

caused by a delayed starting time of the EBRT boost to the parametrium.

Discussion

This study determined that there was favorable radiotherapy compliance with the JGOG1066 protocol. Based on our findings, we expect the final results of this study on long-term outcomes and complications to be scientifically valid.

A credentialing process was used to select the participating institutions in this study. Our credentialing consisted of a review of questionnaires received from institutions and an assessment of radiotherapy QA, especially with regard to HDR-ICBT. The credentialing process has been adopted for some recent clinical trials performed by the Gynecologic Oncology Group (GOG). Lowenstein and colleagues reported that major protocol deviations were more frequently seen in non-certified institutions than in certified institutions [11]. We believe that the credentialing process in this study may be one of the reasons that favorable protocol compliance was achieved.

Favorable radiotherapy compliance was observed for EBRT, especially with regard to parameters defined by numerically prescribed values, such as beam energy and prescribed dose, which had 100% compliance. Regarding EBRT port arrangements, deviations were observed in 6 patients. These were all from a single institution and were based on CTV delineation-based treatment planning. Only 2-dimensional (2D) treatment planning was prescribed in the protocol. Some clinical study groups have published consensus guidelines for CTV delineation of the pelvic node region [12, 13], and the Radiation Therapy Oncology Group (RTOG) has also released a guideline for primary cervical cancer tumors [14]. For future clinical trials, it will be essential to include detailed descriptions of 3-dimensional (3D) treatment planning, including the definition of CTV contouring. In this study, frequent deviations were observed for EBRT boosts. Most deviations were omissions at the discretion of the treating physicians, despite indications for a boost. These physicians might have prioritized their clinical impressions and experiences over the protocol. We believe that there was a discrepancy between the protocol and current daily clinical practice. At present, there is no obvious evidence that an EBRT boost provides therapeutic value [15]. In ongoing Gynecology Oncology Group (GOG) and RTOG trials, EBRT boosts have been optional. Therefore, for trials in the near future, it is reasonable to keep the EBRT boost as an option.

Although protocol compliance was also favorable for HDR-ICBT administration, 4 violations were seen. Two were in patients who received their first HDR-ICBT application before they received 30 Gy of EBRT. Eligible patients in this study all had extensive cervical disease. It is thought that locoregionally advanced disease should receive adequate doses of EBRT before HDR-ICBT application, and it is essential to deliver an adequate HDR-ICBT dose to the entire cervical tumor [16]. There was 1 patient who received EBRT and HDR-ICBT on the same day, which was judged as a violation. In accordance with the ABS guidelines [6], concurrent delivery of EBRT and HDR-ICBT was strictly prohibited in the protocol. In 1 patient, treatment planning for the first HDR-ICBT was also applied during the subsequent HDR-ICBT sessions. We believe that these types of violations should be strictly avoided, because they could cause poor treatment outcomes and decrease safety [6].

Only 4 deviations were observed for the designation of point A. We adopted 2 alternative determination methods for point A from a previous prospective study (JAROG0401/JROSG04-2) [17]. In that study, 10 of 60 patients were assessed with deviations regarding the definition of point A [17]. We think that compliance with this definition has improved over the previous study. To further improve compliance with point A determination, a dummy run may be effective. This would also be effective for CTV delineation on EBRT treatment planning. While image-guided brachytherapy is becoming popular, especially in the United States [18], point A is still widely used for dose prescription along with DVH parameters [19]. We think that our system can provide consistent and clinically appropriate point A determinations [20].

The theoretical weakness of our present QA process is lack of physics QA, including an external dosimetry audit and independent dose calculation of HDR-ICBT. In the GOG and RTOG studies, an independent HDR-ICBT dose calculation was performed and revealed some variation of actual doses compared with prescribed doses [20]. We need to establish an effective QA system for physics by ensuring active participation of medical physicists in the CCRT studies of cervical cancer. Our QA assessments regarding deviations and violations may be considered subjective. We classified the cases into 3 QA categories based on previously decided criteria. Our QA criteria were developed with reference to those used in other clinical study groups, such as GOG [11]. Development of standard QA criteria, including those pertaining to physics which can be used globally, should be encouraged.

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

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Conflict of interest No author has any conflict of interest.

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A Consensus-based Guideline Defining Clinical Target Volume for Primary Disease in External Beam Radiotherapy for Intact Uterine Cervical Cancer

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Objective: To develop a consensus-based guideline to define clinical target volume for primary disease (clinical target volume primary) in external beam radiotherapy for intact uterine cervical cancer.

Methods: The working subgroup of the JCOG Radiation Therapy Study Group began developing a guideline for primary clinical target volume in November 2009. The group consisted of 10 radiation oncologists and 2 gynecologic oncologists. The process started with comparing the contouring on computed tomographic images of actual cervical cancer cases among the members. This was followed by a comprehensive literature review that included primary research articles and textbooks as well as information on surgical procedures. Extensive discussion occurred in face-to-face meetings (three occasions) and frequent e-mail communications until a consensus was reached.

Results: The working subgroup reached a consensus on the definition for the clinical target volume primary. The clinical target volume primary consists of the gross tumor volume, uterine cervix, uterine corpus, parametrium, vagina and ovaries. Definitions for these component structures were determined. Anatomical boundaries in all directions were defined for the parametrium. Examples delineating these boundaries were prepared for the posterior border of the parametrium for various clinical situations (i.e. central tumor bulk, degree of parametrial involvement).

Conclusions: A consensus-based guideline defining the clinical target volume primary was developed for external beam radiotherapy for intact uterine cervical cancer. This guideline will serve as a template for radiotherapy protocols in future clinical trials. It may also be used in actual clinical practice in the setting of highly precise external beam radiotherapy, including intensity-modulated radiotherapy.

Key words: cervical cancer – radiation therapy – clinical target volume – contouring

INTRODUCTION

Standard radiotherapy for cervical cancer patients consists of external beam whole pelvic radiotherapy (EBRT) and intracavitary brachytherapy (1). Recently, treatment planning for both modalities has been shifting away from conventional two-dimensional planning to volume-based three-dimensional (3D) planning (2,3). Three-dimensional planning should achieve appropriate target coverage within sufficient doses and effective sparing of organs at risk (OARs). Intensity-modulated radiation therapy (IMRT) is the most promising 3D EBRT method, and its use has been increasing in actual clinical practice in the USA (4) and other countries. Several investigators reported promising treatment results in terms of reduced toxicity for patients with uterine cervical cancer (5–7). In Japan, IMRT has been covered by the public insurance system since April 2010 for all cancer patients. Therefore, as is now the case for other solid malignancies, the use of IMRT should be promoted for cervical cancer patients. To correctly deliver IMRT, an accurate and reproducible contouring of the clinical target volume (CTV) is primarily important and essential. There is, however, a degree of uncertainty in the delineation of the CTV (8). To achieve consistent CTV delineations, which minimize unexpected variation, consensus guidelines have been published for the pelvic lymph node CTV (9–11). A working subgroup for developing a consensus-based guideline on the CTV for cervical cancer was organized within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG) in July 2008. The subgroup has already published a guideline on pelvic node CTV (12). More recently, the Radiation Therapy Oncology Group (RTOG) in the USA published guidelines regarding primary tumor CTV (CTV primary) for intact uterine cervical cancer (13). We have also conducted a study to establish a CTV primary guideline to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT. This paper describes the process used to develop the guideline, as well as examples of CTV delineation schemes.

PATIENTS AND METHODS

The working subgroup, which was formed to establish a consensus-based guideline on the CTV for EBRT in cervical cancer, started working on the CTV for primary lesions (CTV primary) in November 2009. In addition to the original seven members, five members consisting of three radiation oncologists and two gynecologic oncologists joined the committee. The members had three face-to-face meetings and extensive discussions via e-mail throughout the working process.

In the first meeting, a brainstorming discussion was held with review of the CTV definitions of image-guided intracavitary brachytherapy (IGBT) for cervical cancer (14–16), and the CTV primaries of other disease sites, e.g. head and neck, and prostate (17). After this meeting, electronic copies of computed tomographic (CT) and magnetic resonance imaging (MRI) images of two actual patients were distributed to the members. Each member then independently made his or her own CTV primary delineations on the CT images. The contoured images were then reviewed in the second meeting. Some areas of discrepancy were observed in the CTV primary delineations (Fig. 1a and b). Following extensive discussion to reach consensus, drafts of the definitions of structures composing the CTV primary and actual figures were prepared by a principal investigator (T.T.) referring to the RTOG guidelines (13). These were presented and reviewed at the JCOG RTSG meeting in November 2010. These were then refined further through additional e-mail discussions. A consensus among the working group members was nearly reached in the third meeting. Any remaining discrepancies were addressed through subsequent e-mail discussions. A final version of the consensus-based guideline on the CTV primary was established in February 2011.

RESULTS

Components for the CTV Primary

The CTV primary consists of the gross tumor volume of the primary tumor (GTV primary), uterine cervix, uterine corpus, parametrium, vagina and ovaries.

Definitions for Each Component Structure of the CTV Primary

GTV Primary

The GTV primary includes gross disease visible on an MRI T2-weighted image (T2WI) and lesions detected by clinical examinations.

Uterine Cervix

The entire cervix, if not already included within the GTV contour, is to be contoured (13). The cranial margin is defined at the level at which the uterine arteries enter the uterus (same level of the superior border of the parametrium CTV).

Uterine Corpus

No CTV margin should be added to the visualized corpus on CT images, even for cases in which the tumor has significant corpus invasion. This decision was based on the fact that the majority of the uterine corpus is suspended within the pelvic cavity without surrounding the connective tissue.

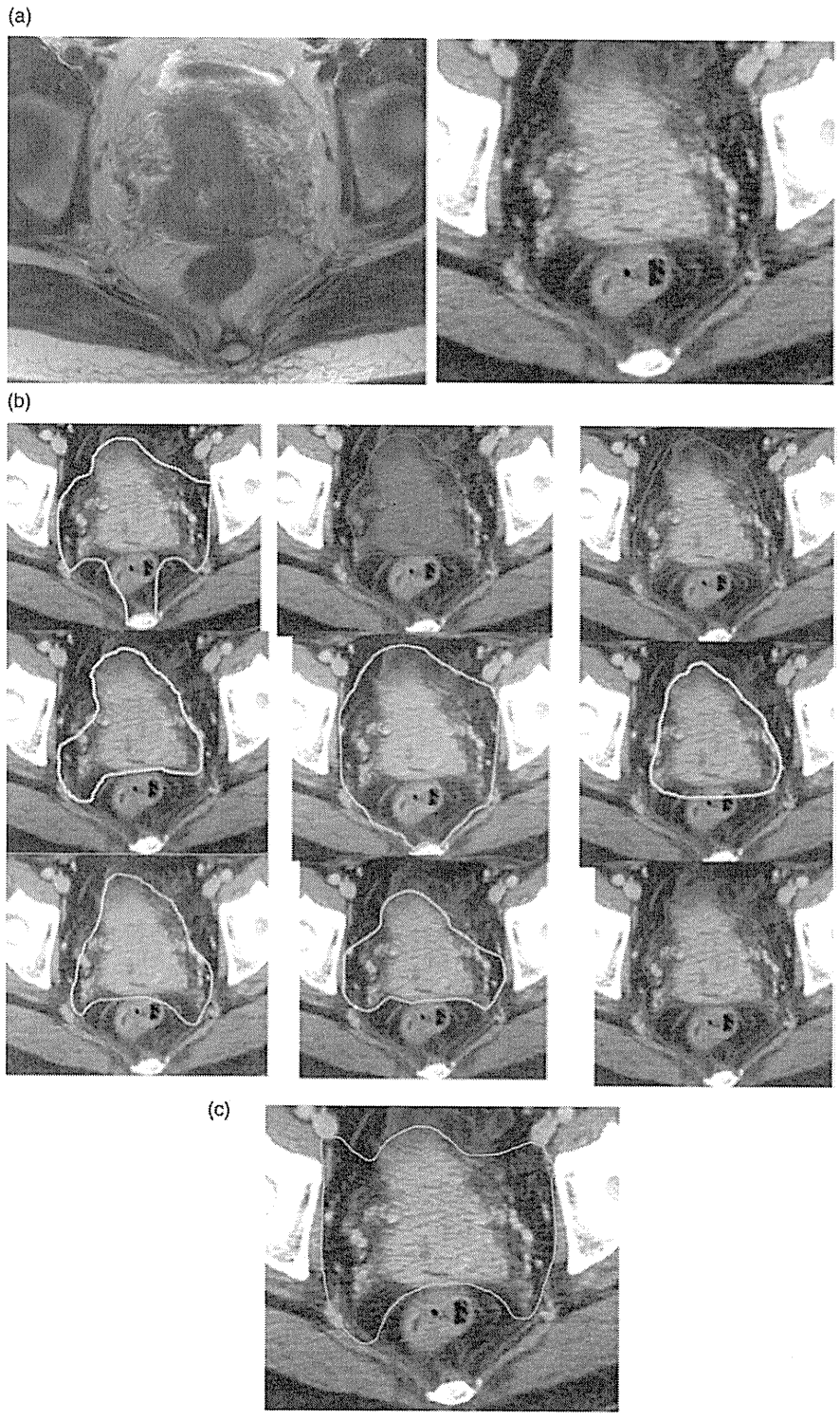

Figure 1. (a) Magnetic resonance imaging (MRI) and computed tomographic (CT) slices of a FIGO Stage IIIB cervical cancer patient who demonstrated bilateral parametrial invasion with nodular fixation to the right pelvic wall on pelvic exam. Clinical information for this patient was also distributed to the nine working group members along with the CT and MRI images. (b) CT images with the primary clinical target volume (CTV) contouring drawn by the working group members, which reveal substantial contouring variations among the members. (c) The same CT image with the primary CTV contouring following the present guideline.

Table 1. Anatomical boundaries of clinical target volume for parametrium

Margin	Structures
Cranial	Isthmus of uterus (=level where uterine artery drains into)
	*Contouring would stop at the level where bowel loops are seen
Caudal	Medial boarder of levator ani (Fig. 5)
Anterior	Posterior boarder of bladder or posterior boarder of external iliac vessels
Posterior	Anterior part (semicircular) of mesorectal fascia
	*In case with bulky central tumor or significant parametrial invasion, some modification would be considered (Figs 3 and 4)
Lateral	Medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ischial ramus

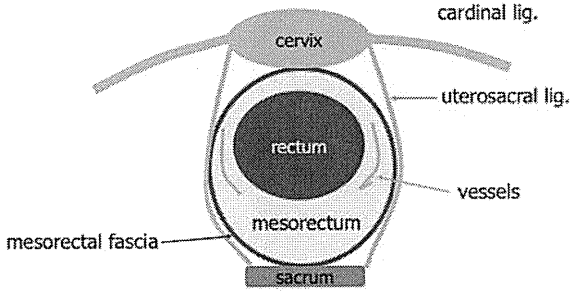

Figure 2. An illustration of the anatomical components around the cervix with reference to the parametrium.

The broad ligaments, round ligaments and ovarian ligaments do not need to be included.

Consensus was not reached regarding feasibility of excluding some portions of the uterine corpus (e.g. fundus) from the CTV primary in selected cases (i.e. non-bulky Stage I or II cases who may be candidates for radical trachelectomy).

Parametrium

Adipose tissues between the cervix and pelvic wall are included as well as visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures).

Overlapping between the nodal CTV and the parametrium CTV is feasible (13).

Boundary structures of the parametrium CTV for each direction are listed in Table 1. Figure 2 shows a scheme of anatomical components around the cervix with reference to the parametrium. Figures 3a and 4a show a scheme and actual delineation for the posterior border of the parametrium, respectively. Some variations are prepared as determined by the central tumor bulk or parametrial involvement status for the posterior boundary of the parametrium CTV (Figs 3 and 4). The CTV margin could be increased in the posterior direction into the perirectum (Figs 3b and 4b) and/or along the uterosacral ligaments (Figs 3c and d, and 4c and d). Figure 5 shows the primary CTV contouring at the level of the levator ani.

Vagina

Paravaginal tissue would be included as well as the vaginal wall. The caudal level should be individually determined based on the findings of both the MRI and clinical examinations. Arrangements of the caudal level according to the status of vaginal invasion are stated as per the RTOG guidelines (13):

Minimal or no vaginal extension: upper half of the vagina
Upper vaginal involvement: upper two-thirds of the vagina
Extensive vaginal involvement: entire vagina

Ovary

Ovaries visible on the CT/MRI would be included.

A consensus was not reached regarding the possibility of excluding the ovaries in selected cases (i.e. non-bulky Stage I or II cases with squamous cell carcinoma).

An Example of the CTV Primary Delineation (Fig. 1c)

Figure 1c shows an example of the CTV primary delineation in accordance with the definition developed (on the same slice used in the previous comparison test).

DISCUSSION

The working subgroup developed a consensus-based guideline for the delineation of the CTV primary for EBRT in patients with intact uterine cervical cancer. The guideline describes the anatomical components to be included in the CTV primary, as well as the definitions for each component. Examples of CTV delineation are also included.

The guideline states that the CTV primary consists of the GTV primary, uterine cervix, uterine corpus, parametrium, vagina and ovaries. This concept seems to be almost the same with surgical treatment: radical hysterectomy, which is a standard surgical procedure for invasive cervical cancer, also includes resection of these structures.

Anatomically, the uterine corpus is concealed within the broad ligament and suspended in the pelvis. This means that no surrounding connective tissues are visible around the corpus on CT or MRI. Therefore, the guideline states that no margin should be added to the visualized corpus for the CTV. We also reached a consensus that the fallopian tubes and round ligaments would not be included in the CTV, in agreement with the RTOG guidelines (13).

The most challenging issue was delineating the parametrium and defining its anatomical boundaries on CT. This difficulty was caused by the limited information of diagnostic radiology to illustrate the relationship between transverse images and the actual parametrial anatomy. In our preliminary comparison of each member's CTV contouring,

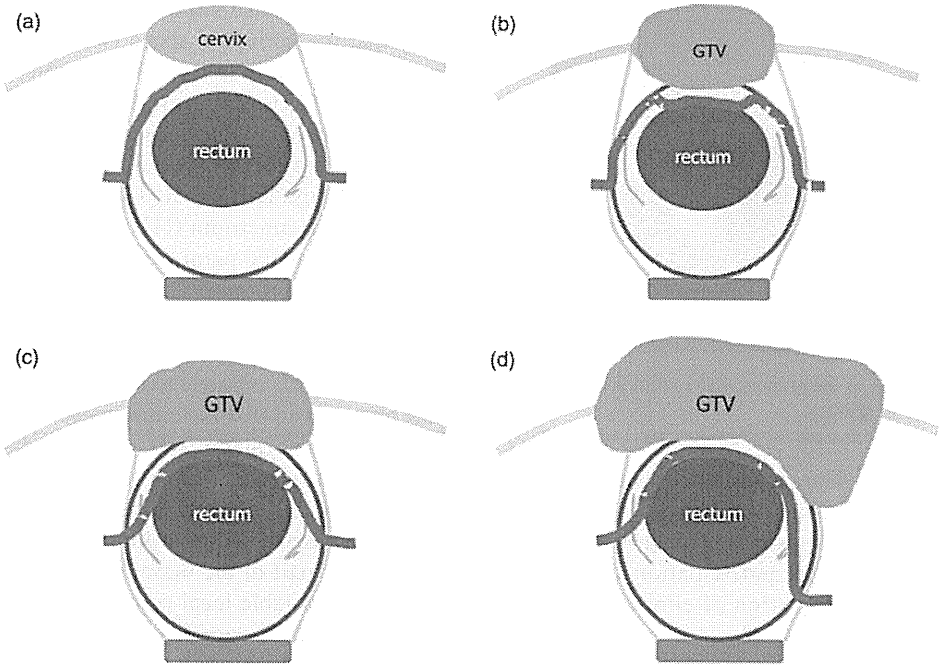

Figure 3. Stage-specific delineation schemes for the posterior border of the parametrium (solid red line). (a) Non-bulky early-stage (IB1 or IIA1) disease. (b) Bulky early-stage (IB2 or IIA2) disease. (c) Stage IIB disease (slight parametrial involvement). (d) Stage IIIB disease (massive parametrial involvement).

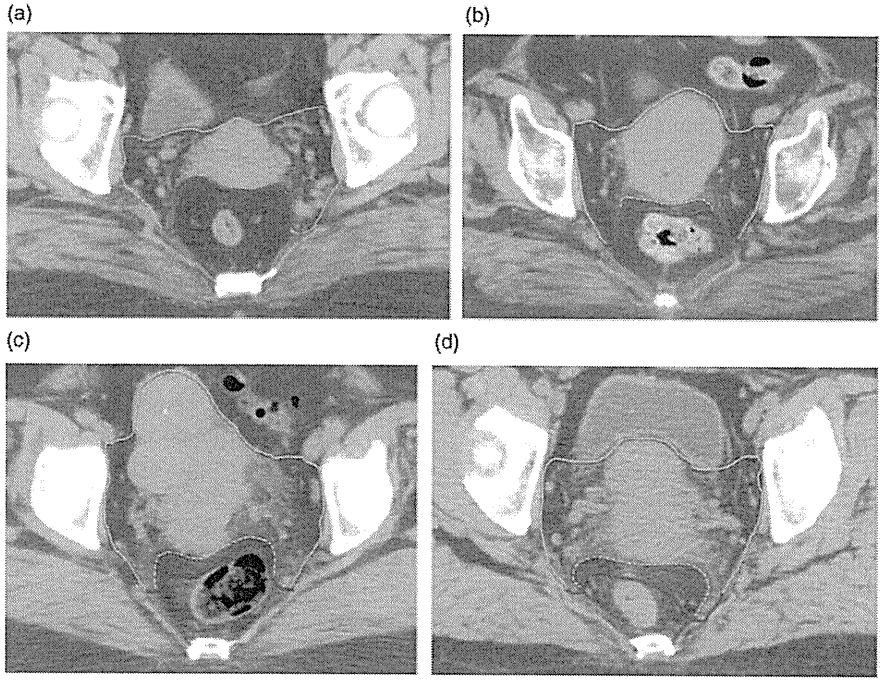

Figure 4. Actual delineations of the primary CTV (solid orange line) and posterior border of the parametrium (solid red line) according to disease status Dotted orange lines indicate the anterior border of the perirectum. (a) A case with non-bulky Stage IB1 disease. (b) A case with bulky Stage IB2 disease. (c) A case with Stage IIB disease (bilateral parametrial involvement on pelvic exam). (d) A case with Stage IIIB disease (massive parametrial involvement with fixation to the left pelvic wall on pelvic exam).

significant variations were observed for the parametrium. Lim et al. (13) reported a similar wide range of variation among the WG members in the RTOG. The present discrepancies were resolved through reviewing the anatomical (18–20) and surgical (21) literatures. In the present work, two gynecologic oncologists participated in addition

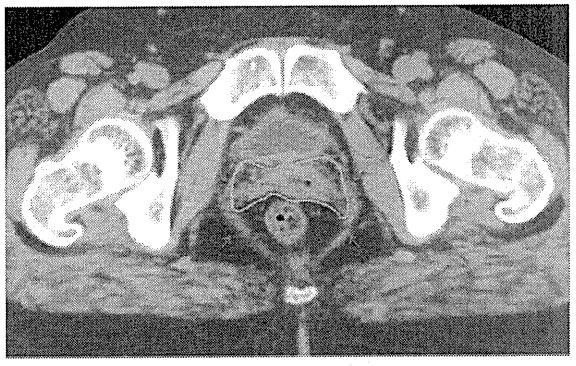

Figure 5. An actual delineation of the primary CTV (solid orange line) at the level of the levator ani (blue arrows).

to the radiation oncologists. They contributed valuable information regarding surgical findings, which was instrumental for developing anatomically appropriate definitions of the boundaries. We believe that the participation of surgical oncologists is essential for the design of clinically reliable CTV definitions and contouring atlases.

The anterior and lateral boundaries are virtually identical to those specified by the RTOG guidelines (13). Minor adjustments were made to the lateral definition in the present guideline. The medial edges of the piriformis and coccygeus muscles were added to the lateral boundary. The RTOG guidelines state that the caudal margin of the parametrium is the urogenital diaphragm (13). However, the term 'urogenital diaphragm' usually indicates the inferior surface of the pelvic diaphragm. Therefore, we consider the superior surface of the pelvic diaphragm, which corresponds to the medial edge of the levator ani, a more appropriate term for the definition.

To determine the cranial boundary of the parametrium, we also reviewed the anatomy of the uterus and surrounding structures including the parametrium. The broad ligaments are formed by the peritoneum covering the uterine body and the parametrium (18,20). Instead of using the top of the fallopian tube/broad ligament for the cranial parametrial margin, as specified in the RTOG guidelines (13), we elected to use the cranial margin of the cervix. In an anatomical view, this margin corresponds to the isthmus of the uterus (18); however, the margin is not recognized on CT images. Therefore, the junction of the uterine artery with the uterus was proposed to be the cranial margin of the cervix. This parameter must be evaluated further clinically to ascertain the degree of variability associated with this definition.

There was extensive discussion concerning the posterior boundary of the parametrium. The RTOG guidelines use the uterosacral ligament as one of the boundaries (13). The uterosacral ligaments, however, are not always identifiable on CT images. In contrast, the mesorectal fascia is visible on the CT images in most cases. Chen et al. (22) have demonstrated that 95 and 97.5% of the CT and MRI studies, respectively, show the fascia encircling the rectum and perirectal adipose tissue as either a continuous or interrupted line. They have also shown in a cadaveric space perfusion study that the perirectal space is completely separated from the pararectal space (outside the mesorectum) by the mesorectal fascia (22). Therefore, we selected the semicircular, anterior portion of the mesorectal fascia as the posterior boundary. The RTOG guidelines include an optional definition for Stage IIIB cases (13). We also include additional areas in the parametrium CTV in cases with a bulky cervical tumor or extensive parametrial involvement. Furthermore, we developed protocol variations to address specific situations. Chao et al. (23) stressed the importance of delivering an adequate dose to the uterosacral space for patients with uterosacral space involvement. In contrast, the RTOG guidelines recommend that the entire mesorectal space be included for patients with Stage IIIB or higher disease. We consider this to be excessive. Kato et al. (24) reported clinical outcomes for locally advanced cervical cancer patients (Stage IIB–IVA) treated with carbon ion radiotherapy. Although the posterior part of the mesorectum was not included within the CTVs, favorable local control was reported in their series (24). These results appear to support our opinion. Careful evaluation is warranted to determine whether the entire mesorectal space should be included in the CTV for patients with massive parametrial involvement, and additional discussion is still required to achieve a consensus.

Another challenge in the development of the guideline is the subdefinition of the CTV primary according to the disease status of each patient. Three-dimensional EBRT, notably IMRT, has the ability to precisely exclude structures not intended to be irradiated. There are at least two potential areas for individualization of the CTV primary in uterine cervical cancer. The first is to permit the exclusion of the ovaries. If the ovaries were excluded from the CTV primary, the planning target volume (PTV) would be smaller. The small PTV may result in lower doses and volumes delivered to the surrounding OARs. This option is feasible as several surgical studies have demonstrated that patients with early-stage cervical squamous cell cancer rarely have ovarian metastases (25,26). The second issue pertains to whether a portion of the uterine corpus may be excluded from the CTV primary. Uterine corpus exclusion may also achieve a significant decrease in the doses to the surrounding OARs. As mentioned in the previous RTOG guidelines (13), excluding a portion of the corpus would be an option for selected cases when sufficient data are available regarding the incidence and exact location of uterine recurrence after conservative surgical procedures (e.g. radical trachelectomy) (27). Although we were not able to reach a consensus on these issues, the discussion continues. For these situations, subdivision of the CTV based on risk estimation of disease (i.e. high-, intermediate- and low-risk CTV) may be considered. The CTV primary definitions on IGBT may serve as a reference for this concept (14,15).

Although the CTV delineation for 3D EBRT planning is performed primarily based on CT/MRI findings, some small or superficial lesions may only be detected by a clinical

examination. These small/superficial lesions should also be included in the GTV. This has been addressed in the present guideline. Generally, the CTV delineation is performed on CT images. It is, however, sometimes difficult to accurately contour the CTV due to low soft tissue resolution of CT. The working subgroup recommends the use of MRI T2WI as a reference. Even with MRI, it is sometimes difficult to perform CTV contouring in thin women who have little adipose tissue in the pelvis. Solving this problem remains a challenge.

In conclusion, we propose that the present consensus-based guideline be used as a reference to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT for intact cervical cancer patients. The use of the present guideline in combination with the previously published guideline for the node (12) will minimize variation in the CTV contouring process. Additional discussion is still required to achieve a consensus regarding how much individualization will be permissible within the guideline. To perform appropriate IMRT, as well as accurate CTV contouring, consensus on the delineation of the OARs is important. Management of organ movement and tumor shrinkage over the treatment course represent additional challenges (28). Further substantial discussions are warranted to define the PTV margins for each CTV primary substructure. The working group needs to continue to develop additional consensus-based guidelines for the precise delivery of IMRT for patients with intact uterine cervical cancer.

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Conflict of interest statement

None declared.

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Appendix

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CLINICAL INVESTIGATION **Gynecologic Cancer**

PROSPECTIVE MULTI-INSTITUTIONAL STUDY OF DEFINITIVE RADIOTHERAPY WITH HIGH-DOSE-RATE INTRACAVITARY BRACHYTHERAPY IN PATIENTS WITH NONBULKY (<4-CM) STAGE I AND II UTERINE CERVICAL CANCER (JAROG0401/JROSG04-2)

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Purpose: **To determine the efficacy of a definitive radiotherapy protocol using high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative dose schedule in nonbulky early-stage cervical cancer patients, we conducted a prospective multi-institutional study.**

Methods and Materials: **Eligible patients had squamous cell carcinoma of the intact uterine cervix, Federation of Gynecologic Oncology and Obstetrics (FIGO) stages Ib1, IIa, and IIb, tumor size <40 mm in diameter (assessed by T2-weighted magnetic resonance imaging), and no pelvic/para-aortic lymphadenopathy. The treatment protocol consisted of whole-pelvis external beam radiotherapy (EBRT) of 20 Gy/10 fractions, pelvic EBRT with midline block of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions (at point A). The cumulative biologically effective dose (BED) was 62 Gy_{10} ($\alpha/\beta = 10$) at point A. The primary endpoint was the 2-year pelvic disease progression-free (PDPF) rate. All patients received a radiotherapy quality assurance review.**

Results: **Between September 2004 and July 2007, 60 eligible patients were enrolled. Thirty-six patients were assessed with FIGO stage Ib1; 12 patients with stage IIa; and 12 patients with stage IIb. Median tumor diameter was 28 mm (range, 6–39 mm). Median overall treatment time was 43 days. Median follow-up was 49 months (range, 7–72 months). Seven patients developed recurrences: 3 patients had pelvic recurrences (2 central, 1 nodal), and 4 patients had distant metastases. The 2-year PDPF was 96% (95% confidence interval [CI], 92%–100%). The**

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2-year disease-free and overall survival rates were 90% (95% CI, 82%–98%) and 95% (95% CI, 89%–100%), respectively. The 2-year late complication rates (according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer of Grade ≥1) were 18% (95% CI, 8%–28%) for large intestine/rectum, 4% (95% CI, 0%–8%) for small intestine, and 0% for bladder. No Grade ≥3 cases were observed for genitourinary/gastrointestinal late complications.

Conclusions: These results suggest that definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED, 62 Gy_{10} at point A) can provide excellent local control without severe toxicity in nonbulky (<4-cm) early-stage cervical cancer. © 2012 Elsevier Inc.

Carcinoma of the cervix, Radiotherapy, High-dose-rate, Intracavitary brachytherapy, Dose response.

INTRODUCTION

Numerous retrospective studies of definitive radiotherapy (RT) have reported favorable local control with an acceptable level of toxicity for patients with early-stage cervical cancer (1–4). A randomized clinical trial (RCT) performed in Italy in the 1990s revealed no significant difference in overall survival between patients treated with surgery and those treated with definitive RT (5). As a result, definitive radiotherapy has been accepted as one of the treatment options for early-stage cervical cancer (6).

Standard definitive RT for uterine cervical cancer consists of external beam RT (EBRT) to the whole pelvis and intracavitary brachytherapy (ICBT) (6). Several RCTs have demonstrated that high-dose-rate ICBT (HDR-ICBT) achieves rates of local control and late toxicity that are similar to those of low-dose-rate ICBT (LDR-ICBT) (7,8). Therefore, HDR-ICBT will likely replace LDR-ICBT as the standard of treatment, with several advantages over the LDR-ICBT. Dosing schedules of HDR-ICBT (*i.e.*, total dose and fractions in combination with EBRT) differ substantially among various countries, both in clinical practice (3, 4, 7–20) and in published guidelines (21, 22). Table 1 lists various schedules for definitive RT with HDR-ICBT along with pelvic control rates for stage I and II cervical cancer (3, 4, 7–22). Immediately evident is the lack of a clear dose-response relationship between biologically effective dose (BED) at point A and pelvic control, which has been previously noted (23).

We have identified two possible factors that explain the lack of a clear dose-response relationship in these retrospective studies. The first is potential bias in the doses delivered to each patient; that is, patients with a poor response to RT might have received higher total doses than good responders. Second, most of these studies did not include tumor size assessment, which was another serious limitation for comparison among the various series. Tumor size is one of the most important parameters affecting local control in radiotherapy for cervical cancer and may vary widely even within the same Federation of Gynecologic Oncology and Obstetrics (FIGO) stage (24). Therefore, a prospective study based on appropriate tumor size assessment and a fixed dose schedule would seem warranted to determine an optimum dosing schedule of HDR-ICBT.

Magnetic resonance imaging (MRI) is one of the most useful imaging modalities to evaluate tumor size objectively in cervical cancer (25–27). Toita *et al.* (28) retrospectively analyzed the relationship between local control and tumor diameter as assessed by MRI in a small series. In that series, in patients with American Brachytherapy Society (ABS)-defined early disease (stage I/II, <4 cm) (22), the 3-year actuarial pelvic control rate was 96%, within the dose range of 48 Gy_{10} to 77 Gy_{10} (28). Pelvic control rates by BED values were 5 out of 5 (5/5) for 48 Gy_{10}, 7/7 for 62 Gy_{10} (α/β = 10), 2/2 for 68 Gy_{10}, and 8/9 for 77 Gy_{10} (28). As shown in Table 1, Japanese investigators have reported favorable pelvic control rates with a total BED of 46 to 68 Gy_{10} despite no objective tumor size assessment. These findings suggest that a cumulative dose of 46 to 68 Gy_{10} may be adequate to achieve local control of nonbulky (<4-cm) early-stage cervical cancer.

Based on the above background data, the Japanese Radiation Oncology Study Group (JROSG; http://www.jrosg.jp) conducted a prospective multi-institutional study to assess the efficacy and toxicity of a definitive RT schedule with low cumulative doses in patients with nonbulky stage I and II uterine cervical cancer. We report herein the endpoint results of that prospective study.

METHODS AND MATERIALS

Patient eligibility criteria

Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix and FIGO stage Ib1, IIa, or IIb disease. Study patients were between 20 and 85 years of age. A complete physical examination, a pelvic examination performed without anesthesia, and a chest X-ray were required to determine the clinical stage. Patients also were required to have cervical tumors less than 40 mm in diameter, assessed by T_2-weighted MRI, and negative pelvic and para-aortic lymph nodes (less than 10 mm in shortest diameter), as determined by computed tomography (CT). The CT and MRI studies had to be preformed within 4 weeks of entry. Patients were also required to have a Zubrod performance score (PS) of 0 to 2 and adequate bone marrow function: white blood cell count ≥3,000/mm^3, absolute neutrophil count ≥1,000/mm^3, and hemoglobin level ≥8.0 g/L (data after transfusion would be acceptable). All patients provided written informed consent.

Protocol treatment

The treatment is shown in Fig. 1, consisting of a combination of EBRT and HDR-ICBT. Interstitial brachytherapy was not allowed. Chemotherapy was also not permitted. EBRT was delivered to a total dose of 50 Gy in 25 fractions over 5 to 6 weeks. The initial 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvis field with a midline block (MB) 3 to 4 cm in width. The MB was formed with multileaf collimators (MLC) or a custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. If HDR-ICBT could not be performed in this time interval, the protocol was

Table 1. Schedules and doses of definitive radiotherapy using HDR-ICBT for stage I and/or II cervical cancer

Study (country) (ref)	EBRT (Gy)	HDR-ICBT dose (Gy/fr) or dose range at point A	Total BED (Gy_{10}) or BED range at point A	% or % range of pelvic control (follow-up)	Median follow-up	Comments
Reports						
Nakano *et al.* (Japan) (4)	0–20	29/5–23/4	46–62	86[§]	22 years	Stage IB and II (small)
Teshima *et al.* (Japan) (7)	20	28/4–30/4	63–66	87[§]	11 years	Stage I and II (all)
Hareyama *et al.* (Japan) (8)	0–30	29/5–23/4	46–68	89 (5 years)[‡]	47 months	Stage II (all)
Wang *et al.* (Taiwan) (9)	39.6–45	24/5	82–88	87–94 (5 years)[‡]	5 years	Stage I and II (all)
Wong *et al.* (China) (10)	40	21/3–24/4	84–86	79–89 (5 years)[‡]	4.7 years	Stage I and II (all)
Ozsaran *et al.* (Turkey) (11)	50.4	18/3	88	73 (5 years)[‡]	42 months	CCRT data; stage I and II (all) = 82%
Lee *et al.* (Korea) (3)	40	39/13	95 (median)	95[§]	60 months	Stage IB
Souhami *et al.* (Canada) (12)	45	24/3	96	80–88[§]	50 months	Including CCRT data
Petereit *et al.* (US) (13)	40–50*	45.5–49.5/5[†]	96 (median)[†]	88 (3 years)[‡]	22 months	Stage I and II (≤5 cm)
Sood *et al.* (US) (14)	45	18/2	87	77 (3 years)[§]	3 years	Stage I and II (all): 87%
Anker *et al.* (US) (15)	45	30/5	101	97 (3 years)[‡]	25 months	Including CCRT data; stage I and II (all) = 80%
Patterns of care						
Toita *et al.* (Japan) (16)	30	22–23/4	70–72	–	–	Stage I and II (all)
Jones *et al.* (UK) (17)	40–60	7.5/1–42/6	61–96	–	–	Small volume
Pearce *et al.* (Canada) (18)	45	30/5	101	–	–	Same in all stages
Erickson *et al.* (US) (19)	NS	NS	103 (median)	–	–	All stages combined
Dyk *et al.* (Australia, New Zealand) (20)	45–60	18/3–30/5	73–94	–	–	All stages combined
Recommendations						
Okawa (Japan) (21)	0, 20	29/5, 23/4	46, 60	–	–	Stage I and II (small)
Nag *et al.* (US [ABS]) (22)	20, 45	48/8, 30/5	101	–	–	Stage I and II (nonbulky, <4cm)

Abbreviations: EBRT = external beam radiotherapy; HDR-ICBT = high dose-rate intracavitary brachytherapy; BED = biologically effective dose CCRT = concurrent chemoradiotherapy; fr = fraction; NS = not stated; ABS = American Brachytherapy Society.

* 1.7 Gy/fr.

† Point M.

‡ Actuarial rate.

§ Crude rate.

terminated, and any subsequent treatments (*e.g.*, additional whole-pelvis EBRT without the MB) were at the discretion of the treating physician. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 6 MV or greater. Both anteroposterior (AP)-posteroanterior (PA) and a four-field techniques were allowed. When the four-field technique was utilized, the portal arrangement was changed to the AP/PA technique after the MB was inserted. A tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4-L5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1 to 2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was placed at a horizontal line drawn 1 cm anterior to the symphysis pubis anteriorly and a vertical line at the posterior border of the sacrum posteriorly. The upper and lower borders were the same as those for the AP/PA fields. The fields were shaped to shield normal tissues, using a custom block or MLC. Prophylactic para-aortic radiotherapy was not allowed.

HDR-ICBT was performed once per week, administering 24 Gy to point A in four fractions with Ir-192 afterloading machines.

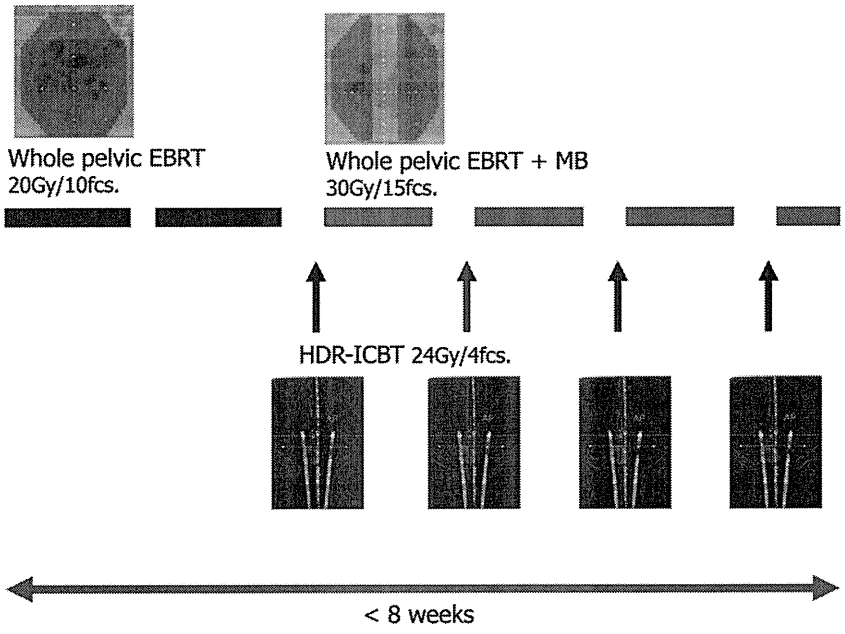

Fig. 1. Treatment schema.

HDR-ICBT delivery was not allowed on the same day as the EBRT. A combination of tandem and ovoid applicators was recommended except as restricted by the vaginal anatomy (*e.g.*, narrow vagina) or significant vaginal disease invasion. Source dwell patterns (*i.e.*, times and positions) were determined according to the Manchester system(29). For determining point A, two alternative rules were established on the basis of the topographical relationships between the tandem and ovoid applicators (30). First, for two A points (left and right), the point associated with the lower dose was to be designated as the prescribed point A. The second rule pertained to the point of origin for the determination of point A. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) would be selected as the geographic origin of the point A. In the event the external os was located caudally to the cranial ovoid surface (*e.g.*, roomy vaginal vault), a coordinate of the vaginal vault surface was to be designated as the origin of the vertical level to point A. The concept behind the latter definition is essentially the same as that for point H, proposed by the ABS (22). Dosimetry was performed before each application,using two orthogonal radiographs. The isodoses were plotted, and the doses to the rectum and bladder were calculated according to International Commission on Radiation Units and Measurements (ICRU) 38 criteria (31). Three-dimensional planning with CT and/or MRI was not utilized.

RT was postponed until adverse effects resolved, if one or more of the following adverse events was observed: Grade 4 hematologic toxicity; Grade ≥3 diarrhea, cystitis, nausea, and/or dermatitis; and PS ≥3. If the grade of the toxicities did not decrease after 3 weeks, the planned treatment was terminated.

Quality assurance (QA) reviews of the RT were performed by the QA committee for all patients entered. Treatment charts and radiological data and figures were submitted and reviewed. The results have been published elsewhere (30). Tumor diameter was also reevaluated for all patients at the time of the QA meetings.

Evaluation

Acute side effects were scored according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Late toxicity was scored by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity criteria. Patients visited every 3 months during the first 2 years and then every 6 months or annually. Follow-up was to include assessment of late toxicity, pelvic examination, CT of the abdomen and pelvis (every 6 months), MRI of the pelvis (every 6 months), and chest X-ray (every 6 months).

Statistical analysis

The study was approved by the JROSG Protocol Review Committee and the local institutional review boards of the participating institutions.

The primary purpose of this study was to determine if the RT protocol could achieve a local control rate comparable to those previously reported in several retrospective studies. The primary endpoint of this study was the 2-year pelvic disease progression-free (PDPF) rate. Sample size was calculated on the basis of the primary endpoint. We set the expected level for the 2-year PDPF at 85%. To achieve the result within a 95% confidence interval (CI, 75%–95%)for the 2-year PDPF, we calculated that 54 patients would have to be recruited over 3 years, based on the Brookmeyer-Crowly method (32). After the sample size was adjusted by 10% to allow for patient ineligibility or loss, the total sample size was 60 patients.

The secondary endpoints were acute toxicity, treatment completion rate, late complication rate, 2-year disease-specific survival (DSS) rate, 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate, and site of recurrence. The PDPF, DSS, DFS, and OS endpoints were measured from the date of treatment start to the date of the events. Estimates of survival distribution and late complication probability were calculated by the Kaplan-Meier method. All analyses were performed using SAS version 8.02 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. No patient was assessed as

Table 2. Patient characteristics

Characteristics	No. of patients (%)
Age (years)	
Median	73
Range	37–84
<60	11 (18)
60–70	11 (18)
70–80	31 (52)
>80	7 (12)
Performance status	
0	31
1	28
2	1
FIGO stage	
Ib1	36 (60)
IIa	12 (20)
IIb	12 (20)
Tumor size (mm)	
Median	28
Range	6–39
<10	2 (3)
10–19	5 (8)
20–29	23 (39)
30–39	22 (37)
Unable to measure	8 (13)

ineligible. Therefore, 60 patients formed the patient cohort for the analysis. Pretreatment characteristics for the eligible patients are listed in Table 2.

Acute toxicity and compliance

Forty-four patients (72%) were treated on an inpatient basis. The acute toxicity profiles during and after the protocol treatment period (within 90 days) are shown in Table 3. Only one patient experienced toxicity necessitating treatment rest (Grade 3 diarrhea); however, per the patient's treating physician, no protocol treatment postponement was adopted. Eleven patients had treatment rest (median, 4 days; range, 1–7 days). Five patients had treatment rest because of national holidays; 4 patients because of machine trouble; 1 patient because of heart disease; and 1 patient because of preference. Overall treatment time (OTT) ranged from 38 to 55 days, with a median of 43 days. All 60 patients (100%) completed the planned protocol treatment.

Efficacy

Two patients (3%) were lost to follow-up (at 7 and 10 months) within the 24-month follow-up interval. The remaining 58 patients were followed beyond the planned 24 months. The median follow-up time for all 60 patients was 49 months (range, 7–72 months).

Table 3. Acute toxicities

	No. of patients by toxicity grade (n = 60)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	17	16	3	0
Neutropenia	15	5	3	0
Anemia	14	2	0	0
Thrombocytopenia	13	0	0	0
Dermatitis	17	4	0	0
Nausea	10	0	0	0
Diarrhea	25	11	1	0
Cystitis	8	5	0	0

Three patients experienced pelvic recurrence: 2 patients had central recurrence, and 1 patient had recurrence in lymph nodes. The estimated 2-year and 3-year PDPF rates were both 96% (95% CI, 92%–100%) (Fig. 2). Five patients developed distant metastases: 4 patients had metastases without pelvic recurrence, and 1 patient had metastases after pelvic recurrence. These cases included recurrence in paraaortic lymph nodes (1 patient), lung (1 patient), liver and subcutaneous tissue (1 patient), and multiple osseous lesions and nodes (2 patients).

Figure 3 shows the incidence of pelvic recurrence and distant recurrence as a function of tumor size subcategories. No pelvic recurrences occurred in patients with tumors less than 30 mm in diameter. The incidence of distant metastasis rose as tumor diameter increased.

Of the 5 patient deaths recorded, 4 patients died from cervical cancer, and 1 patient without cervical cancer recurrence died from an unrelated cause. The estimated 2-year and 3-year DFS rates were both 90% (95% CI, 82%–98%), and the estimated 2-year and 3-year OS rates were both 95% (95% CI, 89%–100%) (Fig. 2).

Dose to organs at risk and late toxicity

In ICBT, median calculated doses to the rectum and bladder according to the ICRU 38 definition were 4.9 Gy (range, 2.2–10.5 Gy) and 4.8 Gy (range, 2.1–12.1 Gy), respectively. Table 4 lists gastrointestinal and genitourinary late toxicity profiles. No patient suffered severe gastrointestinal or genitourinary late toxicities (Grade ≥3). The estimated 2-year and 3-years rates for late toxicities (Grade 1–2) were 16% (95% CI, 6%–26%) and 18% (95% CI, 8%–28%) for the large intestine and rectum, respectively; 0% and 2% (95% CI, 0%–5%), respectively, for the bladder; and 4% (95% CI, 0%–8%) and 7% (95% CI, 4%–14%), respectively, for the small intestine (Fig. 4).

DISCUSSION

To our knowledge, this is the first multi-institutional prospective study to evaluate the efficacy and toxicity of a defined radiotherapy schedule with HDR-ICBT for uterine cervical cancer. Our prospective study demonstrated good 2-year and 3-year PDPF rates of 96% (95% CI, 92%–100%) and an acceptable level of toxicity in 60 patients with nonbulky (<4-cm, assessed by MRI) stage I and II cervical cancer. These results suggest the clinical validity of previously reported results of other Japanese studies (4, 7, 8, 28).

The study by Petereit and Pearcey (23) questioned the published favorable data from Japanese investigators with low cumulative radiotherapy doses, noting that the doses in those Japanese series were less than tumoricidal. The BED of 62 Gy_{10} utilized in our study is equivalent to the 52 Gy used in conventional fractionated radiotherapy (33).

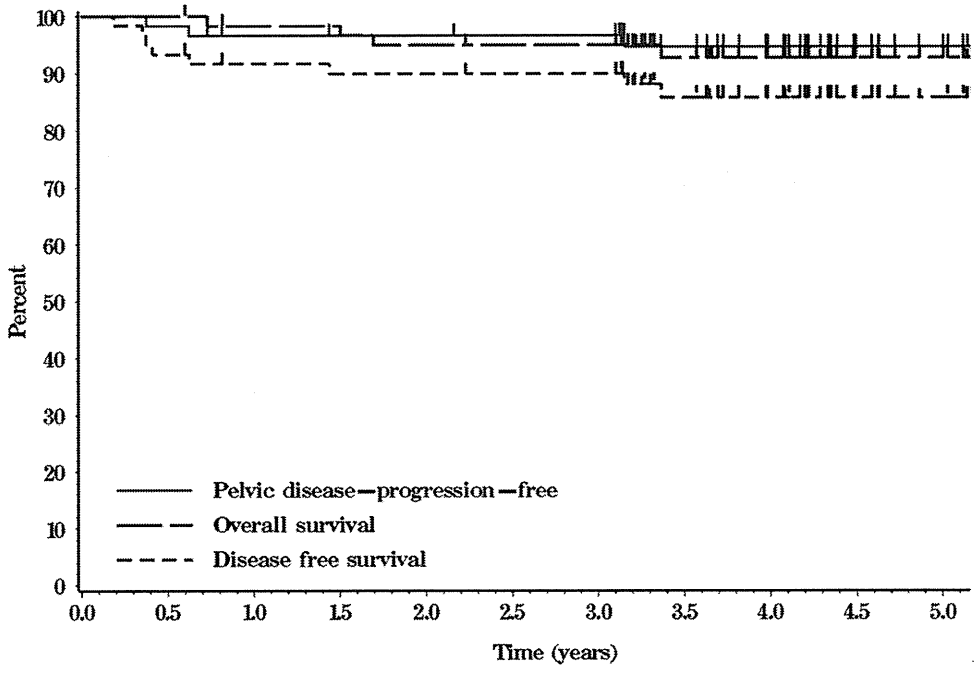

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

As Petereit and Pearcey (23) claimed, 52 Gy is the minimum dose for eradicating subclinical microscopic disease (*i.e.*, low risk clinical target volume). However, in the definitive radiotherapy for cervical cancer, the dose distribution of ICBT with a steep dose gradient should be taken into account in analyzing dose response on local control. In some patients with small volume tumor, the minimum dose delivered to the tumor might be higher than a prescribed point A dose.

In addition to radiation physics issues, radiobiological parameters need to be taken into account to explain the favorable local control results, despite the low radiation dose delivered in our study. One potentially significant parameter is the short OTT in our study. The OTT has been reported to be one of the most important treatment factors affecting local control of cervical cancer (34). In our study, the relatively short median OTT (median, 43 days) might have positively affected the local control results. Fowler and colleagues (35) proposed a linear quadratic formula that takes time factors in account. Several investigators have demonstrated that the repopulation rate of cervical cancer cells increases at around 21 to 28 days after starting EBRT (36). Our treatment protocol specified that HDR-ICBT was to start at 2 to 3 weeks. Additionally, tumor cell heterogeneity in radiosensitivity and tumor volume have been implicated as important factors affecting tumor control probability in sophisticated radiobiological models (37). In our series, no patients with small tumors (<2–3 cm) developed local recurrence. This finding is supportive of the hypothesis that a lower dose might be sufficient for eradicating cancer cells in small volume tumors,

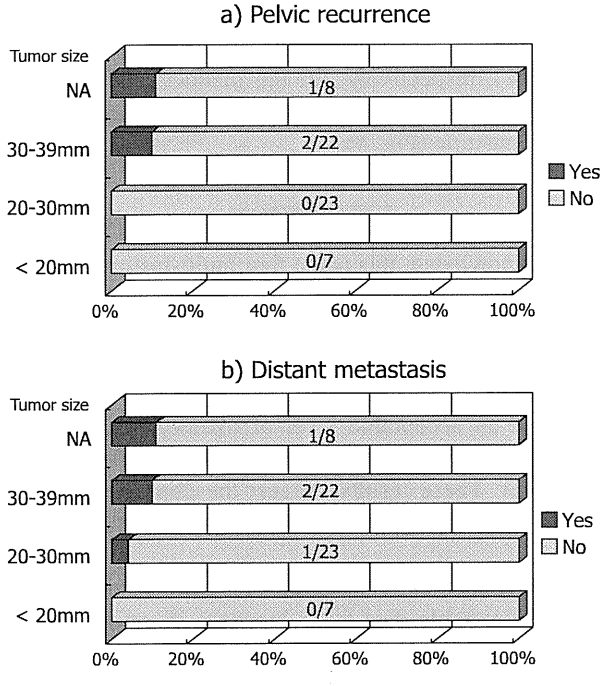

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

Table 4. Late toxicities

Toxicity	No. of patients by toxicity grade (n = 60)			
	Grade 1	Grade 2	Grade 3	Grade 4
Small intestine	3	1	0	0
Large intestine/rectum	9	2	0	0
Bladder	0	1	0	0

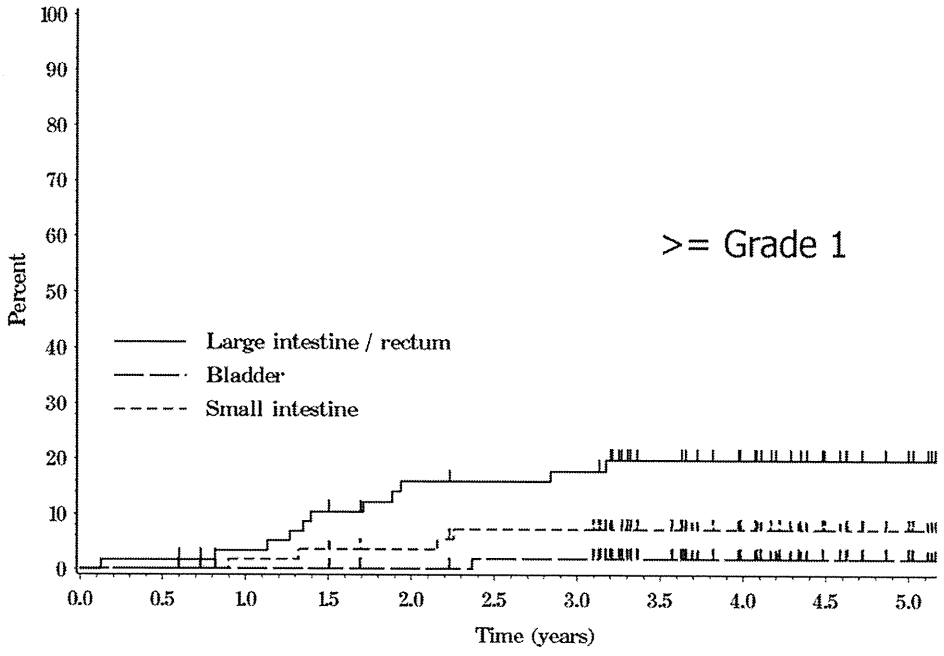

Fig. 4. Late complications (Grade ≥1) are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

even if such a low dose is not effective in treating bulky tumors.

In our study, acute and late toxicities were also evaluated prospectively. We assessed the incidence and grade of acute toxicities among our study patients as acceptable. Regarding late toxicities, no patient suffered severe gastrointestinal or genitourinary complications (Grade ≥3). We would consider this outcome to be a positive consequence of the low cumulative doses delivered to the central pelvis.

One potential limitation to our study was that the application of a MB might have introduced some degree of uncertainty with respect to the EBRT dose to the cervical tumor (38). This uncertainty resulted from the difficulty in confirming that the MB completely covered the cervix in every patient during every EBRT fraction in this study. Recently, onboard CT images have now become routinely available in clinical practice. Daily confirmation with this imaging device is feasible to confirm that an MB completely covers the cervical lesion.

CONCLUSIONS

In conclusion, the results of our study suggest that definitive radiotherapy consisting of whole-pelvis EBRT of 20 Gy/10 fractions, pelvic EBRT with an MB of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions at point A (BED 62 Gy_{10}) is an effective and safe treatment for stage I and II cervical cancer patients with small (<4-cm) tumor diameter. Recently, the value of dose-volume histogram parameters for predicting local control in MR image-guided BT has been investigated for treating cervical cancer (39, 40). A future prospective study with the novel image-guided BT method using appropriate dose-volume histogram parameters is encouraged to confirm the findings of the present study in the near future.

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