A surveillance study of intensity-modulated radiation therapy for postoperative cervical cancer in Japan

Naoya Murakami1*, Hiroyuki Okamoto1, Fumiaki Isohashi2, Keiko Murofushi3, Tatsuya Ohno4, Daisaku Yoshida5, Makoto Saito6, Koji Inaba1, Yoshinori Ito1, Takafumi Toita7 and Jun Itami1

1Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-8045, Japan
2Department of Radiation Oncology, Osaka University Hospital, Suita, Osaka
3Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki
4Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma
5Department of Radiology, Gunma Prefecture Cancer Center, Gunma
6Department of Radiation Oncology, Chiba Cancer Center, Chiba
7Department of Radiology, Graduate School of Medicine, University of Ryukyus, Okinawa

*Corresponding author. Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-8045, Japan.
Tel: +81-3-3542-2511; Fax: +81-3-3545-3567. Email: namuraka@ncc.go.jp
Received July 25, 2014; Revised February 8, 2015; Accepted March 10, 2015

ABSTRACT

Intensity-modulated radiation therapy (IMRT) was recently introduced to the field of gynecologic malignancies; however, its value is not yet validated. A clinical trial is in preparation to investigate the efficacy and feasibility of IMRT for post-operative cervical cancer. The object of this study was to perform a surveillance study of IMRT for post-operative cervical cancer. A questionnaire regarding the precise methods of conducting IMRT was sent to six institutions that had already introduced IMRT for post-operative cervical cancer, and the data were analyzed. Half of the institutions used static IMRT and the others used volumetric-modulated arc therapy (VMAT). Most institutions used body-immobilizing devices for patient fixation. Most institutions instructed patients to fill their bladder before undergoing planning CT or daily treatment. While one institution inserted metallic markers and another one used radio-contrast–soaked gauze to visualize the vaginal cuff, the other institutions used nothing for vaginal cuff visualization. Most institutions defined the clinical target volumes according to the Japan Clinical Oncology Group or the Radiation Therapy Oncology Group guidelines. Only one institution used a prescribed dose based on 95% of the PTV (D95), while the rest used the mean dose (Dmean). This valuable information from six leading institutions will be utilized in a future prospective clinical trial.

KEYWORDS: intensity-modulated radiation therapy, postoperative adjuvant radiation therapy, cervical cancer, surveillance, Japan

INTRODUCTION

Post-operative radiotherapy is an established adjuvant treatment after radical hysterectomy with intermediate- and high-risk early-stage cervical cancer patients [1, 2]. A conventional radiation technique for post-operative cervical cancer patients is whole-pelvic radiation therapy (WPRT) requiring four static photon fields. This technique exposes most of the contents of the true pelvis, including the small bowel as well as the target volume. The highly conformal technique of intensity-modulated radiation therapy (IMRT) has the potential for delivering the required radiation dose to the target volume, while avoiding surrounding normal tissues, and its effectiveness has been validated in several anatomical sites such as head-and-neck [3, 4] and prostate cancer treatment [5, 6]. However, the advantage of using the complex IMRT technique in the field of gynecologic cancer has not...
yet been determined [7–9] and demands a prospective clinical trial for its validation. The Radiation Therapy Oncology Group (RTOG) launched a multi-institutional prospective Phase II trial (RTOG 0418) using IMRT for post-operative endometrial and cervical patients in order to determine whether IMRT could reduce short-term bowel toxicity. Recently, a positive preliminary result was presented [10]. In Japan, because of the concern about possible severe late bowel complications related to the combination of surgery and radiotherapy, and of a positive result from adjuvant chemotherapy alone for intermediate- and high-risk post-operative cervical cancer patients [11], several institutions dare not use adjuvant radiation therapy for early-stage intermediate- or high-risk post-operative cervical cancer patients. Since the RTOG 0418 trial included not only cervical cancer but also endometrial cancer patients, it was decided that the effectiveness and safety of IMRT should be validated including only post-operative cervical cancer patients in a Japanese multicenter prospective clinical trial. As a preparation for this clinical trial, it was regarded as important to ascertain the current status of IMRT for post-operative cervical cancer in Japan. The object of this study was to perform a surveillance study of IMRT for post-operative cervical cancer in a Working Group within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG).

MATERIALS AND METHODS
In 2013, the Working Group conducted a surveillance using a questionnaire asking about the precise methods of conducting IMRT. Six leading academic institutions in the field of gynecologic oncology, who have already commenced applying IMRT for post-operative cervical cancer patients in clinical practice, were selected for the current survey. The academic institutions included cancer center hospitals and university hospitals. Data collection included: (i) the technical environment for IMRT; (ii) patient preparation before taking planning computed tomography (CT); (iii) the technique for determining the target volume and the normal structure; (iv) the prescription dose, the dose constraint for organs at risk (OARs), how to define the prescription dose; and (v) how patients were set up in daily treatment.

RESULTS
Figure 1 describes the technical environment for IMRT. Half of the institutions used conventional static IMRT, while the others used volumetric-modulated arc therapy (VMAT). One institution used a 15-MV photon beam, which could deliver radiation to deep-seated organs.

Figure 2 summarizes the preparation of patients before taking planning CT. All except one institution used either a vacuum cushion or a shell for patient body fixation, which was important for highly precise radiation therapy as IMRT. One institution used a Baseplate® (O rfi t Ind ustries n.v., Vosveld 9A, 2110 Wijnegem, Belgium), which was capable of fixing a patient’s hips, legs and feet. According to the RTOG 0418 protocol, all except one institution used full bladder CT for treatment planning. In contrast to the RTOG protocol, most of the institutions did not visualize the vaginal cuff before taking planning CT.

Figure 3 shows how physicians define the clinical target volume (CTV). For the elective lymph node region, all institutions used the guideline for pelvic nodal CTV created by the Japan Clinical Oncology Group Gynecologic Cancer Study Group (JCOG–GCSG) [12]. For contouring the vaginal cuff, the paracolpium and the parametrium, which may contain microscopic cancer cells after radical hysterectomy, four institutions used the RTOG guideline [13] for reference, while two institutions used the JCOG–GCSG guideline for the intact uterus [14] with modification, because the uterus no longer existed after surgery. Two institutions used the fusion CT images taken with the bladder full and empty according to the RTOG protocol to account for the internal motion of the CTV vaginal cuff, while others contoured the CTV vaginal cuff based on one CT series, adding a 5–10 mm internal margin.

Figure 4 described the normal structures selected as the OARs in treatment planning. The organs which were commonly selected as OARs were the rectum, the bladder, the femoral head, and the small bowel/peritoneal cavity. One institution contoured the bowel loop, four the peritoneal cavity, and one did not contour either the bowel loop or the peritoneal cavity.

Figure 5 summarizes the total prescription dose and the prescription point. The total prescription dose was either 50 Gy/25 fr in

![Fig. 1. A bar graph summarizes the technical environment for IMRT between institutions.](https://academic.oup.com/jrr/article-abstract/56/4/735/2580313)

![Fig. 2. A bar graph showing the way of patient preparation before taking planning CT.](https://academic.oup.com/jrr/article-abstract/56/4/735/2580313)
2 Gy per fraction or 50.4 Gy/28 fr in 1.8 Gy per fraction. Five institutions used the planning target volume (PTV) $D_{\text{mean}}$ (mean dose of the PTV) as a prescription point, while one institution used PTV $D_{95}$ (lowest dose encompassing 95% of the PTV). As for the dose constraint for OARs, one institution did not set any specific dose constraint. In this institution the attending physician checked the dose distribution and paid careful attention to hot spots in OAR. The other five institutions used the individual dose constraint definition, and this is summarized in Table 1. Preliminary compliance rates of dose constraints for OARs for five to eleven patients treated during the study period are also summarized in Table 1.

With regard to the daily set-up of image-guided radiation therapy (IGRT), three institutions took Cone-Beam CT (CBCT) every day, one three times a week and two once a week. As for the rectum preparation, no institution gave patients an enema before treatment. Three institutions encouraged patients to empty the rectum every day before treatment, whereas no instruction concerning rectum emptying was given to patients in the other three institutions; however, in two out of these three institutions, CBCT was taken every day and if large amounts of gas or stools were found, patients were asked to empty the rectum before irradiation.

Figure 6 shows a typical dose distribution of IMRT for post-operative cervical cancer patients from the six institutions participating in this study.

Fig. 3. A bar graph showing which guidelines physicians used as a reference when contouring the target volumes.

Fig. 4. A bar graph showing which normal structures were selected as organs at risk (OARs).

DISCUSSION
Planning and delivery of radiation therapy have changed dramatically over the past several decades [15], and IMRT is one of the most complicated and error-prone techniques, and thus requires thorough quality assurance programs, not only for multicenter clinical trials but for daily practical use. As a preparation for a future clinical trial using adjuvant IMRT for post-operative cervical cancer patients, it was considered to be important to know the current status of IMRT in terms of post-operative radiotherapy for cervical cancer in Japan; therefore, the current surveillance study was performed.

Half of the institutions used VMAT, for which it was shown that the treatment time will be shortened compared with conventional static IMRT for pelvic irradiation, but a dosimetric benefit would not be expected [16]. One institution used a 15-MV photon beam. The high-energy photon beam has an advantage of delivering photons to deep-seated organs with less attenuation; however, it brings with it a concern about creating neutrons along with photons. In the latest patterns of care study (PCS) for cervical cancer in Japan, the majority of institutions used photon beams of between 10 and 14 MV [17]. The most appropriate machine energy should be discussed for developing the protocol of a future clinical trial.

Although visualization of the vaginal cuff was recommended in the RTOG protocol, most institutions did not visualize them. It was supposed that inserting markers into the vaginal cuff would require manpower, time and patients' endurance of pain. One institution inserted a small piece of gauze soaked with a contrast agent into the vaginal cuff, whereas it was not permitted to insert gauze into the vagina in the RTOG protocol because it would potentially cause anatomical changes relative to the surrounding structures. It was considered to be feasible if only a small piece of gauze was manipulated; however, the impact from volume changes of the bladder and the rectum is considered to be more significant. Therefore, inserting a small piece of gauze with a contrast agent will be included in the protocol of a future clinical trial.

All except one institution used full bladder CT for treatment planning. It was supposed that when the bladder was filled with urine, the bowel would be pushed away from the small pelvis and it would protect the small bowel from radiation exposure. However, reproducibility of bladder filling is problematic because the pelvic nerve plexus has already been damaged to varying degrees by radical hysterectomy; therefore, monitoring daily bladder filling by some means needs to be considered to ensure the accuracy of the treatment.
Table 1. Dose constraint for OAR

<table>
<thead>
<tr>
<th>Institute</th>
<th>Institution A (adherence rate, $n = 10$)</th>
<th>Institution B (adherence rate, $n = 10$)</th>
<th>Institution C (adherence rate, $n = 11$)</th>
<th>Institution D (adherence rate, $n = 5$)</th>
<th>Institution E (adherence rate, $n = 5$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>$V_{50 Gy} &lt; 40%$, $D_{max} &lt; 55 \text{ Gy}$ (80%)</td>
<td>$V_{50 Gy} &lt; 35%$ (80%)</td>
<td>$V_{40 Gy} &lt; 60%$ (18.2%)</td>
<td>$V_{50 Gy} &lt; 35%$ (100%)</td>
<td>$V_{40 Gy} &lt; 80%$ (40%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>$V_{55 Gy} &lt; 50%$, $D_{max} &lt; 55 \text{ Gy}$ (80%)</td>
<td>$V_{55 Gy} &lt; 70%$, $V_{50 Gy} &lt; 35%$ (80%)</td>
<td>$V_{45 Gy} &lt; 35%$ (36.4%)</td>
<td>$V_{50 Gy} &lt; 35%$ (100%)</td>
<td>$V_{45 Gy} &lt; 35%$ (60%)</td>
</tr>
<tr>
<td>Small bowel/</td>
<td>$V_{40 Gy} &lt; 40%$, $V_{55 Gy} &lt; 1 \text{ cc}$ (80%)</td>
<td>$V_{40 Gy} &lt; 40%$ (40%)</td>
<td>$V_{40 Gy} &lt; 30%$ (45.5%)</td>
<td>$V_{40 Gy} &lt; 30%$ (80%)</td>
<td>$V_{40 Gy} &lt; 30%$ (80%)</td>
</tr>
<tr>
<td>peritoneum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral head</td>
<td>$V_{30 Gy} &lt; 20%$ (80%)</td>
<td>$V_{30 Gy} &lt; 15%$ (20%)</td>
<td>$V_{30 Gy} &lt; 15%$ (36.4%)</td>
<td>$D_{mean} &lt; 30 \text{ Gy}$ (80%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic bone</td>
<td>$V_{20 Gy} &lt; 80%$ (80%)</td>
<td></td>
<td></td>
<td></td>
<td>$V_{10 Gy} &lt; 90%$, $V_{40 Gy} &lt; 37%$ (20%)</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>$D_{max} &lt; 50 \text{ Gy}$ (40%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OAR = organ at risk.

All institutions used the JCOG–GCSG guideline [12] as a reference in order to contour the CTV lymph node. The reason why the RTOG guideline [13] was not used as a reference to contour the CTV lymph node was that the definition of the CTV lymph node according to the JCOG–GCSG guideline differed slightly from the RTOG guideline. First, in the JCOG–GCSG guideline, the cranial margin was set at the bifurcation of the aorta, not based on the bony structure as in the RTOG guideline. It would be difficult to categorize the recurrence as a regional (pelvic recurrence) or a distant (para-aortic nodal) failure when the previous pelvic field was constructed based on the bony anatomy. Second, the Japanese guideline involved the adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body, which was not included in the RTOG guideline. This area was also included in the atlas of Taylor et al. [18, 19]. Therefore, the current RTOG definition may be insufficient in terms of lateral expansion of the CTV for the internal iliac node. As for the CTV vaginal cuff, while four institutions used the RTOG guideline [13], two institutions used the JCOG–GCSG guideline for the intact uterus [14]. Not all institutions used the RTOG guideline, because the RTOG guideline did not describe the paracolpium and the parametrium in detail. Although, theoretically, the JCOG–GCSG guideline for the intact uterus was not appropriate for contouring the post-operative female pelvis, the JCOG–GCSG description of the parametrium was more specific than the RTOG guideline. Therefore, this guideline can be used as a reference in contouring the paracolpium and the parametrium after making some modification. We are now creating a consensus-based guideline for CTV vaginal cuff as well as the paracolpium and the parametrium (which may contain microscopic cancer cells, even after R0 radical hysterectomy), because there exists no such consensus guideline other than the RTOG guideline. With regard to the internal organ motion of the CTV vaginal cuff, two institutions used the fusion CT with the bladder full and empty according to the RTOG protocol, while others contoured the CTV vaginal cuff based on one CT series, adding 5–10 mm internal margin to CTV vaginal cuff. The vagina is sandwiched by the rectum and the bladder, whose volume will potentially vary from time to time; therefore, it was considered to be important to make a consensus on the internal margin for the CTV vaginal cuff.

Whereas all but one institution selected the small bowel or the peritoneal cavity as an OAR, with four institutions contouring the peritoneal cavity and one the bowel loop, it was not standardized as to whether to contour only the bowel loop itself or the peritoneal cavity as well. In the current study, four institutions contoured the peritoneal cavity and one the bowel loop. The dose–volume relationship will not be reliable if it is not consistent whether the bowel loop or the peritoneal cavity is contoured. For example, Isohashi et al. demonstrated that a dose–volume relationship was found between chronic gastrointestinal (GI) complications and dose to the small bowel loops, whereas no parameter for the peritoneal cavity was significantly associated with GI complications [20]. On the other hand, some modification of the definition will be required if the peritoneal cavity is to be used as an OAR, because part of the bowels are embedded in the retroperitoneal space, such as the ascending or the descending colon. Therefore, we will also develop a consensus-based definition of what constitutes normal structures for the post-operative cervical cancer patient.

Most institutions did not employ PTV $D_{95}$ as the prescription point for concern about possible dose escalation compared with the conventional dose prescription according to ICRU Report 50 [21]. Consequently, the RTOG 0418 protocol [10], in which PTV $D_{95}$ was used as a prescription dose, was considered to be a more aggressive prescription dose in our Working Group. The dose constraint for OARs and preliminary compliance rates of dose constraints for OARs are summarized in Table 1. Because every institution used individual dose constraints, and contouring of the small bowel/peritoneum was not uniform, a large variation in the actual compliance rate was found. RTOG 0418 [10] reported that 66–76% of patients did not meet the dose criteria for the bladder and the rectum, and the dose constraint was loosened in the next RTOG 1203 protocol because it was considered to be too strict. It is, therefore, important to set achievable and clinically relevant dose constraints as well as to develop a consensus of contours for OARs, especially the small bowel/peritoneum, for a future clinical trial using IMRT for post-operative cervical cancer patients.
Fig. 6. A typical dose distribution of IMRT for postoperative cervical cancer patients from six institutions participating in this study: Institutions A–F (A–F).
The six institutions that contributed to this study were equipped with modern linear accelerators capable of doing CBCT for daily set-up. It is very important to ensure accurate daily patient set-up when using IMRT, which can generate a very steep and complicated dose distribution, especially when applied in such a large field as the pelvic region. If IMRT is to become a standard therapy for post-operative...
cervical cancer, which is unfortunately still a relatively common cancer in our country, many institutions will need to update their accelerators with modern machines; this will contribute to improving the quality of radiation therapy in our country.

The valuable information reported here was derived from six leading institutions in the field of gynecological oncology. This information will be utilized for the improvement of a future prospective clinical trial.

ACKNOWLEDGEMENTS
This article was presented in the 73th Annual meeting of the Japan Radiology Society.

FUNDING
This study was partially supported by the Cancer Research Development Fund (23-A-13, 26-A-4 and 26-A-28). The name of the funding body was the National Cancer Center. Funding to pay the Open Access publication charges for this article was provided by the Cancer Research Development Fund (23-A-13, 26-A-4 and 26-A-28).

REFERENCES