A dummy-run evaluation of post-operative hypofractionated intensity-modulated radiation therapy (POHIM-RT) trials for cervical cancer

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ABSTRACT

The postoperative hypofractionated intensity-modulated radiation therapy (POHIM-RT) trial is a phase II study to evaluate toxicity following hypofractionated intensity modulated radiation therapy (IMRT) for cervical cancer. This study describes the results of a benchmark procedure for RT quality assurance of the POHIM-RT trial. Six participating institutions were provided computed tomography for RT planning and an IMRT plan for a sample and were instructed to delineate volumes, create a treatment plan and quality assurance (QA) plan, and submit the results of all procedures. The inter-institutional agreements on RT volume and plan results were evaluated using the kappa value and dice similarity coefficients. The simultaneous truth and performance level estimation (STAPLE) method was employed to generate a consensus target volume. The treatment volumes, organs-at-risk volumes, and results of the RT plan and QA reported by the institutions were acceptable and adhered well to the protocol. In terms of clinical target volume (CTV) delineation, there were differences between the institutions, particularly in vaginal cuff and paracolpium subites. Consensus CTV was generated from the collected CTVs with the STAPLE method. The participating institutions showed considerable agreement regarding volume, dose and QA results. To improve CTV agreement in CTV, we provided feedback with images of the consensus target volume and detailed written guidelines for specific subites that were the most heterogeneous.

Keywords: cervical cancer; hypofractionation; IMRT

INTRODUCTION

Radical hysterectomy is the standard treatment for early-stage cervical cancer. Postoperative radiotherapy (RT) following hysterectomy has been shown to improve local control and disease-free survival in high-risk patients with more than two risk factors in the surgical pathology: depth of invasion 1/3, lymphovascular invasion or tumor size > 4 cm [1, 2]. RT with concurrent chemotherapy (CCRT) following surgery improves survival for those with a positive resection margin, parametrial invasion or lymph node metastasis [3]. Despite the benefit of postoperative RT in terms of survival, 5 and 15–30% of patients experience acute gastrointestinal, urinary and hematologic toxicity following RT and CCRT, respectively. Acute
treatments are related to the radiation dose to adjacent normal organs, including small intestines, bladder and pelvic bone. Advances in intensity modulated RT (IMRT) techniques have reduced acute toxicities, particularly in the postoperative setting, by sparing the intestines and bladder from irradiation when compared with box techniques [4, 5].

Hypofractionated RT is defined as the delivery of a higher dose per fraction with fewer total fractions. Hypofractionation has the benefit of reducing the overall treatment duration, which can enhance tumor control, improve patients’ convenience and more efficiently use medical resources. However, a higher dose per fraction can also increase the biologic effect on surrounding normal tissues, resulting in higher toxicity rates [6].

Although hypofractionation is not routinely employed for whole pelvic RT, several studies have shown acceptable outcomes and toxicities using 2.7–3.4 Gy per fraction for various pelvic malignancies including rectal cancer, bladder cancer and endometrial/cervical cancer [7–9]. Grade 3 or higher toxicity has not been reported following postoperative whole pelvic RT using 37.8 Gy in 14 fractions plus an RT boost with 14–16 Gy to the vaginal stump in patients with cervical and endometrial cancer [8].

Although a number of studies have reported the outcomes of IMRT with a conventional dose schedule in cervical cancer, the outcomes of hypofractionated RT using IMRT in the postoperative setting have not yet been addressed.

The postoperative hypofractionated intensity-modulated (POHIM)-RT and POHIM-CCRT trials in cervical cancer are phase II studies to assess the treatment outcomes and acute and late toxicities of hypofractionated postoperative RT in cervical cancer patients using IMRT techniques. In this study, we aimed to assess the consensus in target delineation, RT planning and quality assurance (QA) planning among institutions participating in the POHIM trials.

### MATERIALS AND METHODS

#### Study protocol

The primary end point of the POHIM trials is to evaluate the acute toxicities of postoperative hypo-fractionated IMRT in patients who underwent radical hysterectomy for cervical cancer. The secondary end point is to evaluate the late toxicities and progression-free survival rate. Eligible patients were those who had been pathologically confirmed as having cervical cancer and who underwent radical hysterectomy and pelvic lymph node dissection. For the POHIM-RT trial, the participating institutions had to meet more than one of the following criteria: tumor size ≥4 cm, positive lympho-vascular invasion, and invasion depth of more than half of the cervical stroma. For the POHIM-CCRT trial, the participants had to meet more than one of the following criteria: lymph node metastasis, parametrial invasion, and positive resection margin. Patients were excluded if they had positive distant metastasis, a previous history of pelvic RT, radical surgery for cervical cancer more than 3 months ago, neoadjuvant chemoradiotherapy, or a previous history of carcinoma other than thyroid cancer, skin cancer and in situ carcinoma on the cervix. Any type of IMRT including rotational techniques are allowed for this study. The prescribed dose to planning target volume (PTV) is 40 Gy in 16 fractions in both trials. For the POHIM-CCRT trial, the participants underwent weekly cisplatin chemotherapy concurrently with the radiotherapy. Target volume and organs at risk (OAR) contoured according to the Radiation Therapy Oncology Group (RTOG) guidelines was used as reference volume [6, 10]. The dose constraints for OAR per protocol are described in Table 1.

#### Quality assurance procedures

The six institutions participating in the POHIM trials were provided with brief case reports and computed tomography (CT) planning for a sample patient who would have been previously treated for postoperative whole pelvic irradiation, but not included in the trial. The institutions were instructed to delineate the target volumes (clinical target volume (CTV) and PTV) and OAR (bowel, rectum, bladder and femoral head) and prepare an IMRT plan in compliance with the protocol. The institutions submitted Digital Imaging and Communications in Medicine files including treatment volumes, OAR volumes and dose distribution of IMRT plan. Institutions were also asked to complete questionnaires regarding details of the RT simulation, plan and treatment delivery; were provided with IMRT plan data; and were instructed to perform a patient-specific IMRT QA and submit the QA results using gamma criteria (2 mm/2%, 2 mm/3% or 3 mm/3%).

#### Volume agreement analysis

Interobserver agreement on the target and OAR volume was assessed using the Kappa index [11]. Kappa values were calculated using Fleiss’ equations and employing Computational Environment for Radiotherapy Research (CERR) software [12]. The dice similarity coefficient (DSC) was calculated using 3D Slicer software to evaluate the similarity between the participating institutions’ CTV and the CTV based

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**Table 1. Dose constraints for target and OAR in the POHIM-RT study**

| Target/normal organ | Per protocol | Acceptable | Unacceptable |
|---------------------|--------------|------------|--------------|
| PTV                 | 95% ≥ D<sub>95</sub>, 107% < D<sub>max</sub> | 90% ≥ D<sub>95</sub>, 109% < D<sub>max</sub> | < 90% ≥ D<sub>95</sub>, < 109% D<sub>max</sub> |
| Bowel               | ≤ 40 Gy V<sub>35 Gy</sub> ≤ 30% | > 30%, < 70% | ≥ 70% |
| Rectum              | ≤ 80% | > 80%, < 100% | 100% |
| Bladder             | ≤ 35% | < 35%, > 70% | ≥ 70% |
| Femoral head        | < 40 Gy V<sub>35 Gy</sub> < 40% | > 40%, < 80% | ≥ 80% |

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Femoral head D<sub>max</sub> ≤ 40 Gy V<sub>35 Gy</sub> ≤ 30% Treatment volume (PTV) D 99.9 < 107% Target/normal organ Per protocol Acceptable Unacceptable

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on RTOG guidelines [13, 14]. Using the collected volumes provided by the institutions, a consensus CTV was generated employing the simultaneous truth and performance level estimation (STAPLE) algorithm using CERR software [15]. The consensus CTV was generated to represent the collected target volumes with a 95% confidence level by a maximum likelihood estimation.

RESULTS

Treatment procedures
The institutions performed CT simulation with the patients in the supine position and with a full bladder; no specific intervention was employed to control the rectum. Four of the institutions employed volumetric modulated arc therapy while two institutions employed dynamic multi-leaf collimator-IMRT techniques. For the pre-treatment image verification, four institutions employed cone-beam CT and two institutions employed 2-D kV imaging.

Treatment volume, plan and quality assurance agreement
Figure 1 shows the target volumes from the six institutions. The overall kappa value for the CTVs and PTVs of the six institutions was 0.64 and 0.76, respectively. The CTV to PTV margin was 7 mm for all institutions according to the study protocol. The overall kappa values for the bowel, rectum, bladder and femur head volume were 0.71, 0.81, 0.89 and 0.63, respectively. The DSC values for the CTVs from the institutions compared with the reference volume ranged from 0.66 to 0.77, and the mean DSC value for the six institutions was 0.72. Table 2 shows a summary of the dose parameters collected from the final plans from the six institutions. The mean PTV dose ranged from 39.5 to 41.5 Gy, which achieved substantial agreement. The OAR dose results from all institutions adhered well to the protocol. The institutions reported >97% gamma passing rates for 2 mm/2% (one institution), 2 mm/3% (one institution) and 3 mm/3% (four institutions; Table 2).

Consensus CTV
To identify the most discrepant CTV sub-site, we divided the CTV into four sub-sites: common iliac lymphatic area (CTV-CILN), internal and external iliac lymphatic areas (CTV-ILN), pre-sacral area (CTV-PS) and vaginal cuff and paracolpium (CTV-VP). We calculated DSC and kappa values for each sub-site. Each institution calculated the dice coefficients compared with the reference volume for the overall CTV and each CTV sub-site (Fig. 2). The mean coefficient values of CTV-PS and CTV-VP were lower than those of CTV (0.60 vs 0.72, P = 0.004). Supplementary Figure 1, see online supplementary material, shows the consensus CTV generated by the STAPLE method (CTV\textsubscript{STAPLE}). The DSC value CTV\textsubscript{STAPLE} was 0.8, which was higher than the mean DSC of the collected CTVs (0.72, Fig. 3). The DSC value of each sub-site of CTV\textsubscript{STAPLE} was also greater than that of the collected CTVs, except for CTV-ILN (Fig. 3).

DISCUSSION
In recent years, hypofractionated RT has been increasingly applied to solid tumors such as breast cancer, prostate cancer and glioblastoma [16]. The advantages of hypofractionation, such as protracted treatment duration, patients’ convenience and efficient use of medical resources, have been underestimated in pelvic irradiation, mainly because of the classical myth of toxicity risk. IMRT techniques have allowed delivery of a sufficient dose to the target volume while sparing the surrounding normal organs. By using IMRT techniques, hypo-fractionated RT could be safely performed while maintaining the benefits of protracted treatment time in pelvic RT [17]. The POHIM-RT and POHIM-CCRT trials are the first prospective phase II studies evaluating the safety and efficacy of hypofractionated IMRT for cervical cancer in the postoperative setting. To successfully conduct clinical trials involving RT, a QA study is essential for assessing and minimizing the RT-related variations that can affect results, particularly in multicenter-studies [18–20]. This study showed that, in most
Table 2. Summary of statistics for target and normal organ volumes and results of QA from six institutions

| Parameters                      | Results from the six institutions (Gy) |
|---------------------------------|---------------------------------------|
|                                 | 1  | 2  | 3  | 4  | 5  | 6  |
| PTV_D99.9                       | 39.72 | 36.83 | 38.2 | 36.26 | 37.87 | 34.79 |
| PTV_Dmax                        | 42.22 | 43.4 | 42.18 | 42.03 | 42.14 | 44.48 |
| PTV_mean dose                   | 41.1 | 41.5 | 40.9 | 39.5 | 40.4 | 40.0 |
| Bowel_Dmax                      | 41.51 | 42.84 | 41.88 | 41.17 | 40.95 | 40.8 |
| Bowel_V35Gy                     | 15.53 | 15.81 | 19.33 | 15.03 | 19.65 | 0.94 |
| Rectum_V35Gy                    | 63.07 | 58.66 | 33.43 | 16.9 | 51 | 17.3 |
| Bladder_V39Gy                   | 32.94 | 9.81 | 12.19 | 2.99 | 15.91 | 1.13 |
| Left femoral head_Dmax          | 37.01 | 24.61 | 29.78 | 23.74 | 39.04 | 27.99 |
| Right femoral head_Dmax         | 37.53 | 24.16 | 34.47 | 29.9 | 39.42 | 28.97 |
| IMRT QA result                  |                |                |                |                |                |
| Gamma index criteria            | 2 mm/2% | 3 mm/3% | 3 mm/3% | 3 mm/3% | 2 mm/3% | 3 mm/3% |
| Gamma index passing rate        | >90% | >95% | >95% | >95% | >95% | >95% |
| Results of QA                   | 97.6% | 98.5% | 99.8% | 99.3% | 99.6% | 97.0% |

Fig. 2. Dice coefficients of CTV and sub-sites of CTVs compared to reference volume.

Aspects (RT simulation, target and OAR volume, planning and QA), the participating institutions complied with the study protocol. Given that the study’s primary endpoint was to evaluate the acute toxicities of hypofractionated RT, the results of the OAR dose of the RT plan are the most important part and have shown acceptable agreement (kappa > 0.7) in all institutions. One institution delineated the femoral head extended to the femur neck and shaft, resulting in a relatively low kappa value for the femoral head volume. Furthermore, QA is an important issue, particularly in studies using IMRT techniques. The results of the institutions’ QA plan also showed considerable agreement by presenting an extremely narrow spectrum of gamma passing rates (97–99%).

We observed acceptable agreements in the target volume delineations; however, the vaginal cuff and paracolpium were the most heterogeneous sub-site among the institutions. A previous South Korean study that assessed the agreement of target delineations in postoperative RT for cervical cancer [21] also concluded that the largest difference between the institutions was observed in the upper vaginal area. The RTOG guidelines describe the vaginal cuff area as the ‘vaginal cuff and proximal 3 cm upper vaginal’; however, the vaginal cuff is not usually visible in the CT image and is hard to delineate. The definition of the paracolpium in the RTOG guidelines is ‘from vaginal cuff to medial edge of internal obturator muscle/ischial ramus on each side’, which does not indicate the anterior and posterior end (Supplementary Table 1, see online supplementary material). Shortcomings in the RTOG guidelines regarding the delineation of the paracolpium have also been suggested by a Japanese group [22] who proposed a revised guideline for delineating the paracolpium [23]. This study’s results also support the need for a more detailed description of the vaginal cuff and paracolpium subites. Supplementary Table 1 proposes a description for the vaginal cuff and paracolpium.

A marker insertion could help define the vaginal cuff more accurately. However, most institutions do not use a fiducial marker to visualize the vaginal stump in the planning CT, which could be because of disadvantages of marker insertion, such as its labor- and time-intensive nature and patients’ inconvenience. Furthermore, the marker can affect the geometry of the vaginal cuff and surrounding organs, which could impair reproducibility in RT delivery. Accordingly, our institutions employed thin catheters with radiopaque material to visualize the vaginal stump (Supplementary Fig. 2, see online supplementary material). Marker insertion was facilitated by the very thin catheters, and we were able to reduce the patients’ discomfort and setup uncertainty.

Although we used only one case for the survey, the target volume might vary based on the patients’ clinical and pathologic characteristics and individual anatomy. Accordingly, the degree of inter-observer variation could vary according to the patients’ clinical setting and anatomy. Nevertheless, this study helped find the drawbacks in the RTOG guidelines and provide the participating institutions with a recommended CTV volume in the form of images and specified written documents as well. Bi-directional feedback at this early stage could improve the quality of the POHIM-RT and POHIM-CCRT trials.
CONCLUSIONS
This study showed that the participating institutions of the POHIM-RT and POHIM-CCRT trials reached considerable agreement in most aspects of the RT plan. However, to improve the CTV agreement, we suggest a consensus CTV and detailed descriptions on the vaginal cuff area.

SUPPLEMENTARY DATA
Supplementary data is available at RADRES Journal online.

CONFLICT OF INTEREST
None declared.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The Institutional Review Board of Samsung Medical Center approved this study (No. 2017–03–092-019) under registration No. NCT03239613 and NCT03239626 (clinicaltrials.gov). All patients had given consent before enrollment.

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Fig. 3. Comparison between mean dice coefficients of collected CTVs (CTV_{INITIAL}) and the sub-sites of CTV_{INITIAL} and dice coefficients of consensus CTV (CTV_{STAPLE}) and the sub-sites of CTV_{STAPLE}
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