Postoperative pelvic intensity-modulated radiation therapy reduced the incidence of late gastrointestinal complications for uterine cervical cancer patients

Keisuke Tsuchida¹,², Naoya Murakami¹,* , Tomoyasu Kato³, Kae Okuma¹, Hiroyuki Okamoto¹, Taizo Kashihara¹, Kana Takahashi¹, Koji Inaba¹, Hiroshi Igaki¹, Yuko Nakayama¹, Takashi Nakano² and Jun Itami¹

¹Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
²Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi Maebashi 371-8511, Gunma, Japan
³Department of Gynecologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

*Corresponding author. Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan Tel: +81-335422511; Fax: +81-335423815; Email: namuraka@ncc.go.jp

(Received 25 March 2019; revised 21 April 2019; editorial decision 12 May 2019)

ABSTRACT

The aim of the study was to compare incidences of late gastrointestinal adverse events and clinical outcomes between 3D conformal radiation therapy (3D CRT) and intensity-modulated radiation therapy (IMRT) after radical hysterectomy for cervical cancer patients. Between March 2007 and May 2014, 73 cervical cancer patients with high-risk prognostic factors (pelvic lymph node metastasis and/or parametrical invasion) underwent postoperative pelvic radiation therapy (RT) after radical hysterectomy. Of these patients, 33 (45%) and 40 (55%) received 3D CRT and IMRT, respectively. Because the gastrointestinal obstruction rate after postoperative pelvic 3D CRT was high, no concurrent chemotherapy was applied until 2015. The median follow-up period for patients with 3D CRT and IMRT was 82 months (6–113) and 50 months (5–74), respectively. There was no significant difference in overall survival (OS) (4-year OS: 85% vs 78%, P = 0.744) or disease-free survival (DFS) (4-year DFS: 73% vs 64%, P = 0.696) between the two groups. Eleven (33%) and 13 (33%) patients experienced recurrence after 3D CRT and IMRT, respectively. Because the gastrointestinal obstruction rate after postoperative pelvic 3D CRT was high, no concurrent chemotherapy was applied until 2015. The median follow-up period for patients with 3D CRT and IMRT was 82 months (6–113) and 50 months (5–74), respectively. There was no significant difference in overall survival (OS) (4-year OS: 85% vs 78%, P = 0.744) or disease-free survival (DFS) (4-year DFS: 73% vs 64%, P = 0.696) between the two groups. Eleven (33%) and 13 (33%) patients experienced recurrence after 3D CRT and IMRT, respectively. The patients who had vaginal invasion from the postoperative pathological finding more frequently had loco-regional recurrence than the patients who did not have vaginal invasion (2.3% vs 17%, P = 0.033). Gastrointestinal obstruction was observed in 9 (27%) and 3 (7.5%) patients for 3D CRT and for IMRT, respectively (P = 0.026). Severe gastrointestinal obstruction that required surgery was observed in 6 (19%) patients, all of whom received adjuvant RT by 3D CRT. IMRT could reduce the incidence of late severe gastrointestinal obstruction after postoperative pelvic RT with a non-inferior clinical efficacy compared with 3D CRT.

Keywords: uterine cervical cancer; postoperative radiation therapy; intensity-modulated radiation therapy; late adverse effects; ileus

INTRODUCTION

Postoperative pelvic radiation therapy (RT) improves outcome in cervical cancer patients with intermediate- or high-risk prognostic factors after radical hysterectomy [1, 2]. However, acute and late toxicities have been noted in the patients treated with radical hysterectomy followed by postoperative pelvic RT. Especially, late gastrointestinal (GI) obstruction is one of the most serious adverse events [1, 3]. Although postoperative pelvic RT is a standard therapy after radical hysterectomy for intermediate- and high-risk early-stage cervical cancer [1, 2], due to the concern for the possible late severe GI toxicities related to the combination of laparotomy and pelvic radiation, and recent emerging positive results from adjuvant...
chemotherapy alone for intermediate- and high-risk post-hysterectomy cervical cancer [4], several Japanese hospitals have not dared to apply postoperative pelvic RT [5]. Intensity modulated radiation therapy (IMRT) can reduce the volume of the small bowel that receives a high dose of radiation compared with 3D conformal radiation therapy (3DCRT), which theoretically could reduce the incidence of GI obstruction. In the Radiation Therapy Oncology Group (RTOG) Trial 1203, which sought to test the feasibility of delivering IMRT in a multi-institutional study of the treatment of gynecologic carcinoma in the post-operative setting, it was revealed that IMRT caused fewer short-term GI adverse events than 3DCRT [6]. However, studies of long-term GI adverse events after IMRT have rarely been reported to date. In this retrospective study, we compared clinical outcomes, incidence of acute and late adverse GI events, and of other adverse events between 3DCRT and IMRT after radical hysterectomy. Additionally, we reported the recurrence patterns of the two radiation methods.

MATERIALS AND METHODS
This retrospective study was approved by the Institutional Ethical Review Board (Approval No. 2017-091) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patients
Between March 2007 and May 2014, patients with uterine cervical cancer undergoing radical hysterectomy and shown to have high-risk prognostic factors [pelvic lymph node (LN) metastasis and/or parametrial invasion] underwent postoperative pelvic RT in our institution. Between March 2007 and August 2010, adjuvant RT was performed by 3DCRT with CT planning and thereafter treated by IMRT.

Radical hysterectomy and bilateral pelvic lymphadenectomy was performed for FIGO Stages IB1, IB2, IIA1, IIA2 and IIB cervical cancer patients in our institution. This procedure involves en bloc removal of the uterus, cervix, and parametrial and paracolpium tissues to the pelvic sidewalls bilaterally, with removal of as much of the uterosacral ligaments as possible. The uterine vessels are ligated at their origin, and the proximal third of the vagina and the paracolpium are resected [7].

We excluded patients with positive surgical margins and/or distant metastases, including para-aortic LN metastases from this retrospective analysis.

Concurrent chemotherapy was not administered during the study period because the incidence of ileus was relatively high after postoperative pelvic RT with 3DCRT.

Radiation therapy
The four box fields of 3DCRT were set up as follows: according to 2D era experience, the following bony landmarks were used for field design using CT image. When patients had tortuous arteries or an extremely large uterus, the field shape was modified to cover an adequate LN drainage area and the entire uterus, based on information obtained from CT. The superior margins were at the intervertebral space between the fourth and fifth lumbar vertebrae, and the inferior margins were at the lower end of the obturator foramen. If the common iliac node was positive for metastasis, the superior margin was placed at the intervertebral space of the second and third lumbar vertebrae. For the AP–PA field borders, the lateral margins were placed at 2 cm lateral to the internal pelvic rim. For the lateral field borders, the posterior border was set in such a way that the entire sacrum was covered. The anterior border of the lateral field was set at a vertical line anterior to the pubic symphysis. The total irradiation dose for 3DCRT was 50 Gy in 25 fractions to the reference point and administered by 15 MV X-rays from Varian linear accelerators (iX, CLINAC, Varian, Palo Alto, California, USA). In the 3DCRT era, no instruction was given to the patients concerning bladder filling.

Regarding the IMRT, the detailed procedure has been described in the reports of our previous studies [8, 9]. A customized immobilization cushion was fabricated to minimize the daily set-up error. Fiducial markers were inserted into the vaginal cuff to visualize it on the CT images [10]. With the patient lying on the immobilization cushion, CT scans with full and empty bladders were taken in order to account for the motion of the vagina as influenced by the contents of the bladder. CT scans of 2-mm slice thickness were taken by an Aquilion LB CT scanner (TOSHIBA Medical Systems, Tokyo, Japan).

The clinical target volume (CTV) was contoured on the individual axial CT slices of each patient. The overall CTV includes both the vaginal cuff/paracolpium CTV and the nodal CTV. The vaginal cuff/paracolpium CTV was contoured in a manner similar to the Radiation Therapy Oncology Group (RTOG) [11] and the Japan Clinical Oncology Group guidelines [9]; cranial margin: 1 cm cranial from the upper part of vaginal cuff metallic marker; anterior margin: posterior border of bladder or retropubic fat pad; posterior margin: anterior part of mesorectal fascia or anterior wall of rectum; lateral margin: medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ishial ramus; caudal margin: 3 cm below the upper part of the vaginal cuff metallic marker. The nodal CTV was based on the Japan Clinical Oncology Group Gynecologic Cancer Study Group (JCOG-GCSG) consensus guidelines for the delineation of CTV for pelvic LNs [12]. The nodal CTV included LNs that drain the involved site and adjacent perinodal soft tissue. This included the internal (obturator and hypogastric), external, and common iliac LNs; the presacral LNs and soft tissues also included down to the level of S3. The upper limit of the nodal CTV was the lumbar vertebra (L) 4/5 interspace. If a common iliac LN metastasis was found pathologically, the nodal CTV was extended to the level of the L2/3 interspace. We used the JCOG-GCSG guideline for reference regarding the nodal CTV because it includes adipose connective tissue between the iliopectineus muscles and the lateral surface of the vertebral body, which is not included in the RTOG guideline [11]. This area is also included in an atlas of Taylor et al. [13, 14]. The CTV was expanded by 5 mm to create the planning target volume (PTV). For normal structures, the small bowel (contoured as a bowel bag, which is defined as the entire peritoneal space), rectum and bladder (both contoured as a whole organ) and the femoral head were routinely contoured according to the RTOG normal tissue contouring guideline [15]. The planning goals of IMRT were to provide a homogenous PTV dose while...
minimizing the dose delivered to the small bowel, bladder and rectum. Dose constraints for the PTV and organ at risks are shown in Table 1.

We compared the volumes of the bowel bag receiving greater than or equal to 15 Gy, 30 Gy, 40 Gy or 45 Gy ($V_{15}$, $V_{30}$, $V_{40}$ and $V_{45}$, respectively) and the bowel bag mean dose ($D_{\text{mean}}$) between 3DCRT and IMRT.

**Evaluation of toxicities**

GI, genitourinary (GU), and hematologic (HT) toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Late morbidity was defined as morbidity seen >3 months after completion of RT. A GI obstruction of Grade 2 or more was counted as an event. Severe GI obstruction requiring surgery was counted separately.

**Statistical analysis**

Differences in clinicopathological factors, dose–volume histogram (DVH) parameters and incidence of acute toxicities between 3DCRT and IMRT were analyzed by the Mann–Whitney U test for quantitative variables and by the Fisher exact test for categorical variables.

The actuarial overall survival rate (OS), disease-free survival rate (DFS), loco-regional control rate (LRC) and incidence of late toxicities were calculated using the Kaplan–Meier method, and differences between groups were compared by the log-rank test. All statistical tests were two-sided, and $P < 0.05$ or a 95% confidence interval (CI) not encompassing 1 was considered as statistically significant.

**RESULTS**

Between March 2007 and May 2014, 73 patients were identified who were treated with radical hysterectomy and postoperative pelvic RT. Thirty-three (45%) and 40 (55%) patients received postoperative pelvic RT by 3DCRT and by IMRT, respectively. The median follow-up period for living patients for 3DCRT and for IMRT was 82 months (6–113) and 50 months (5–74), respectively.

Patient characteristics are summarized in Table 2. The characteristics were similar between the two groups; however, relatively more adenocarcinoma patients were included in the IMRT group (but this was not a statistically significant difference). Seven patients had LN metastasis at the common iliac level; therefore, the upper margin of the radiation field for these patients was set as the intervertebral space between the second and third lumbar vertebrae; four and three patients of this seven were in the 3DCRT and in the IMRT groups, respectively.

There was no significant difference in OS (4-year OS 85% vs 78%, $P = 0.744$) or DFS (4-year DFS 73% vs 64%, $P = 0.696$) between 3DCRT and IMRT, respectively (Fig. 1A and B).

The patterns of recurrence are shown in Table 3. Eleven (30%) and 13 (33%) patients had recurrence after 3DCRT and IMRT, respectively. Four (12%) and 2 (5%) loco-regional pelvic recurrences were seen in 3DCRT and in IMRT, respectively, with no statistically significant difference ($P = 0.270$). All loco-regional recurrences were seen in the vaginal cuff or paracolpium. No recurrence was seen in the pelvic LN area. The patients who had vaginal invasion proven in the postoperative pathological findings had more frequently loco-regional recurrence than the patients who did not have vaginal invasion (17% vs 2.3%, $P = 0.033$) (Fig. 2).

Among 73 patients, GI obstruction was observed in 9 (27%) and 3 (7.5%) patients for 3DCRT and for IMRT, respectively. Two of 9 were from extended-field patients (28.5%) (1 patient from each of the 3DCRT and IMRT groups). Severe GI obstruction that required surgical intervention was observed in 6 patients, all of whom received adjuvant RT by 3DCRT (18% of 3DCRT patients). Small intestine colon bypass and adhesiolysis surgery were performed for 5 patients and 1 patient, respectively. There was a statistically significant difference in the incidence of all grades of GI obstruction (27% vs 7.5%, $P = 0.026$) and GI obstruction that required surgery (18% vs 0%, $P = 0.005$) between 3DCRT and IMRT, respectively (Fig. 3A and B). (Table 4).

The other adverse events are also summarized in Table 4. The incidences of acute GI adverse events, GU adverse events, HT and late leg edema did not differ significantly between 3DCRT and IMRT. However, the incidence of late GU adverse events higher than Grade 2 were significantly more frequently seen in the 3DCRT group (12% vs 0%, $P = 0.038$). Urinary incontinence was mostly seen as a late GU adverse event.

A comparison of DVH parameters for a bowel bag between 3DCRT and IMRT is summarized in Table 5. Bowel bag doses $V_{30}$, $V_{40}$ and $V_{45}$ were significantly lower in IMRT than 3DCRT. However, bowel bag dose did not differ significantly between the patients who developed any grade of GI obstruction and those who did not. Additionally, the bowel bag dose did not differ significantly between the patients who developed serious GI obstruction that required surgery and those who did not.

**DISCUSSION**

Uterine cervical cancer still is a leading cause of cancer incidence and mortality in young women worldwide. Postoperative concurrent
Fig. 1. (A) Kaplan–Meier estimates for comparison of overall survival (OS) between 3DCRT and IMRT groups. (B) Kaplan–Meier estimates for comparison of disease-free survival (DFS) between 3DCRT and IMRT groups.

Table 2. Patients’ clinicopathologic characteristics

|                     | 3D-CRT (n = 33) | IMRT (n = 40) | P-value |
|---------------------|-----------------|--------------|---------|
| Age (years)         | 46 (range 30–66) | 42 (range 28–68) | N.S. |
| Median follow-up period (months) | 82 (range 6–113) | 50 (range 5–74) | <0.001 |
| T stage             |                 | N.S.         |         |
| T1b                 | 8               | 6            | 15      |
| T2a                 | 3               | 5            | 13      |
| T2b                 | 23              | 29           | 72      |
| N stage             | N.S.            |              |         |
| N0                  | 9               | 9            | 23      |
| N1                  | 24              | 31           | 77      |
| Inclusion criteria  | N.S.            |              |         |
| Parametrial invasion + lymph node metastasis | 13 | 39 | 20 | 50 |
| Parametrial invasion | 9 | 27 | 9 | 23 |
| Lymph node metastasis | 11 | 34 | 11 | 37 |
| Histology           | N.S.            |              |         |
| Sq                  | 22              | 21           | 52      |
| AdSq                | 3               | 4            | 10      |
| Ad                  | 8               | 15           | 38      |

3DCRT = three-dimensional conformal radiation therapy, IMRT = intensity-modulated radiation therapy, Sq = squamous cell carcinoma, AdSq = adenosquamous carcinoma, Ad = adenocarcinoma.
chemoradiotherapy (CCRT) for cervical cancer decreases loco-regional recurrence and improves OS rate in patients with high risk factors after radical hysterectomy [1, 3]. However, due to concern for possible occurrence of late severe GI toxicities related to the combination of laparotomy and pelvic radiation, supported by recent emerging positive results for adjuvant chemotherapy alone for intermediate- and high-risk post-hysterectomy cervical cancer [4], several Japanese hospitals have not dared to use PORT for intermediate- and high-risk post-hysterectomy patients [5].

IMRT reduces the volume of the small bowel that receives a high dose of radiation, which potentially leads to reduction of the risks of GI obstruction, while delivering high radiation dose to the target volume. Previous reports have suggested that IMRT reduces acute or late GI adverse events [16–19]. In accordance with previous reports, the current study demonstrated that IMRT could reduce late GI adverse events, especially severe GI obstruction that requires surgical intervention. Acute GI adverse events were not significantly different between IMRT and 3DRT in this study (Table 4).

Regarding other adverse events, Chen et al. [17] showed that IMRT patients had a lower incidence of acute GU toxicities than 3DCRT patients. They also showed that acute HTs and late GU toxicities did not differ significantly between 3DCRT and IMRT. Isohashi et al. [19] showed that acute GU, late GU toxicities and late leg edema did not differ significantly between 3DCRT and IMRT groups. They showed that the IMRT patients had a significantly higher rate of acute Grade 3 hematologic toxicities than the 3DCRT patients. In the present study, the IMRT patients experienced a lower incidence of late GU toxicity greater than Grade 2, with a statistically significant difference (P = 0.038). Radiotherapy is known to cause a fibrotic bladder wall, resulting in a low-compliance bladder, and this is understood to be the cause of the increased incidence of urinary urgency and frequency in patients who have undergone pelvic RT [20, 21]. In this study, it was assumed that the high dose area of the bladder was reduced by IMRT, and that this led to the reduction in the incidence of late GU toxicity. There is a possibility that more patients in the IMRT group received bladder nerve sparing surgery, but this information was not taken into account in this study because the extent of bladder nerve preservation was not always written in the surgical operation records. The incidences of acute HT and late leg edema did not differ between the two radiation methods.

The radiation dose to the bowel can be a predictive factor of GI adverse events in previous reports [22–24]. In this study, we evaluated the radiation dose to the small bowel using a bowel bag as a
The GI obstruction rate in this study was 16.4% (12/73), and that of those who received extended-field EBRT was 28.5% (2/7). Although (possibly because of the limited number of patients with extended field) there was no statistically significant difference \( P = 0.323 \), extended field might have contributed to a higher GI obstruction occurrence.

There is a concern that IMRT may increase loco-regional recurrences by reducing the target volume, in the attempt to protect the bowel. However, previous studies have reported that the oncologic outcome did not deteriorate when using IMRT compared with conventional 3DCRT \[17–19\]. In accordance with these previous reports, the OS and PFS did not differ between 3DCRT and IMRT in this study. No pelvic LN recurrence was seen in either group. All the locoregional recurrences were seen in the vaginal cuff or paracolpium. Furthermore, the recurrences never occurred in the marginal zone of the RT field but in the center of the RT field in both radiation methods. The patients who had a pathologically proven vaginal invasion tend to have local recurrences more frequently. Therefore, dose escalation for the vaginal cuff or paracolpium, especially for patients who have vaginal invasion may contribute to reducing loco-regional recurrences. We consider that boost irradiation using brachytherapy or dose escalation with IMRT (simultaneous integrated boost) for the local region can be a good option for such patients.

Although since 2000 CCRT has been the standard treatment for postoperative uterine cervical cancer patients with high-risk prognostic factors \[1\], concomitant chemotherapy was not administered in our institution during this study period, because, as shown above, the incidence of late GI toxicity was as high as 27% with 3DCRT in our institution, which prevented us using concurrent administration of weekly cisplatin (CDDP). In this context, it can be said that our institution was in a unique position. In such special circumstances, difference between the two different radiation delivery methods alone could be investigated. To the best of our knowledge, this is the first study that has compared 3DCRT with IMRT in the setting of radiotherapy alone. Now that we have shown that IMRT was able to reduce late adverse GI toxicities, CCRT is currently performed in our institution, currently with IMRT. We will compare the outcome for RT alone and CCRT using IMRT in a future study.

### Table 3. Patterns of recurrence after 3DCRT or IMRT

|                      | 3DCRT \( n = 33 \) | IMRT \( n = 40 \) | \( P \)-value |
|----------------------|---------------------|------------------|--------------|
| Loco-regional recurrence | 4 (12.1%) | 2 (5%) | N.S. |
| Vaginal stump or parametrium | 4 (12.1%) | 2 (5%) | N.S. |
| Distant recurrence | 8 (24.2%) | 10 (25%) | N.S. |
| Para-aortic LN | 2 (6.1%) | 3 (7.5%) | N.S. |
| Others | 6 (18.2%) | 7 (17.5%) | N.S. |
| Total | 12 (36.4%) | 12 (30%) | N.S. |

3DCRT = three-dimensional conformal radiation therapy, IMRT = intensity-modulated radiation therapy, LN = lymph node.

### Table 4. Acute and late toxicities in 3DCRT and IMRT patients

|                      | 3DCRT \( n = 33 \) | IMRT \( n = 40 \) | \( P \)-value |
|----------------------|---------------------|------------------|--------------|
| Acute                |                     |                  |              |
| GI                   | \( \geq G2 \) 4 12 | 2 5              | N.S.         |
| G3                   | 0 0                 | 0 0              | N/A          |
| GU                   | \( \geq G2 \) 3 9.1 | 0 0              | N.S.         |
| G3                   | 0 0                 | 0 0              | N/A          |
| Hematologic          | \( \geq G2 \) 19 58 | 21 53            | N.S.         |
| G3                   | 3 9.1               | 2 5              | N.S.         |
| Late                 |                     |                  |              |
| GI                   | \( \geq G2 \) 9 27 | 3 7.5            | 0.026        |
| G3                   | 6 18                | 0 0              | 0.005        |
| GU                   | \( \geq G2 \) 4 12 | 0 0              | 0.038        |
| G3                   | 0 0                 | 0 0              | N/A          |
| Leg edema            | \( \geq G2 \) 5 15 | 8 20             | N.S.         |
| G3                   | 2 6                 | 1 2.5            | N.S.         |

3DCRT = three-dimensional conformal radiation therapy, IMRT = intensity-modulated radiation therapy, GI = gastrointestinal, GU = genitourinary.
There were several limitations to our study. This study was a retrospective study from a single institution with a limited number of patients. The follow-up period differed between the 3DCRT group and the IMRT group. Adjuvant RT alone is not the standard treatment for cervical cancer patients with high-risk prognostic factors after radical hysterectomy, but CCRT is the standard treatment; in this study, all patients were treated with RT alone. However, there are no reports for adjuvant RT alone that compare the efficacy and toxicity of 3DCRT and IMRT. Therefore, we consider that, although the results should be interpreted with caution, this study is important in progressing our understanding of postoperative treatment for cervical cancer.

In conclusion, our results suggested that postoperative pelvic IMRT could reduce the incidence of late severe GI obstruction and demonstrated non-inferior clinical efficacy compared with conventional 3DCRT in patients with uterine cervical cancer.

ACKNOWLEDGEMENTS

Part of this study was presented in the 54th annual meeting of the Japan Society of Clinical Oncology.

CONFLICT OF INTEREST

The authors state that they have no conflicts of interest to declare.

FUNDING

This work was partially supported by the Japan Agency for Medical Research and Development (AMED) and the National Cancer Center Research and Development Fund (26-A-18 and 26-A-28), and the Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan for programs for Leading Graduate Schools, Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering.

REFERENCES

1. Peters WA III, Liu PY, Barrett RJ II et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606–13.
2. Ryu SY, Park SI, Nam BH et al. Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors? *Int J Radiat Oncol Biol Phys* 2011;79:794–9.
3. Monk BJ, Wang J, Im S et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol* 2005;96:721–8.

4. Takeshima N, Umayahara K, Fujiwara K et al. Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB–IIA cervical cancer. *Gynecol Oncol* 2006;103:618–22.

5. Mikami M, Aoki Y, Sakamoto M et al. Surgical principles for managing stage IB2, IIA2, and IIB uterine cervical cancer (bulky tumors) in Japan. A survey of the Japanese Gynecologic Oncology Group. *Int J Gynecol Cancer* 2014;24:1333–40.

6. Klopp AH, Yeung AR, Deshmukh S et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology RTOG 1203. *J Clin Oncol* 2018;36:2538–44.

7. Piver MS, Ghomi A. The twenty-first century role of Piver–Rutledge type III radical hysterectomy and FIGO stage IA, IB1, and IB2 cervical cancer in the era of robotic surgery: a personal perspective. *J Gynecol Oncol* 2010;30:219–24.

8. Murakami N, Okamoto H, Kasamatsu T et al. A dosimetric analysis of intensity-modulated radiation therapy with bone marrow sparing for cervical cancer. *Anticancer Res* 2014;34:5091–8.

9. Murakami N, Norihisa Y, Isohashi F et al. Proposed definition of the vaginal cuff and paracolpium clinical target volume in postoperative uterine cervical cancer. *Pract Radiat Oncol* 2016;6:5–11.

10. Okamoto H, Murakami N, Carvajal CC et al. Positional uncertainty of vaginal cuff and feasibility of implementing portable bladder scanner in postoperative cervical cancer patients. *Phys Med* 2018;45:1–5.

11. Small W Jr, Mell LK, Anderson P et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:428–34.

12. Toita T, Ohno T, Kaneyasu Y et al. A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. *Ipn J Clin Oncol* 2010;40:456–63.

13. Taylor A, Rockall AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1604–12.

14. Taylor A, Powell ME. Conformal and intensity-modulated radiotherapy for cervical cancer. *Clin Oncol (R Coll Radiol)* 2008;20:417–25.

15. Gay HA, Barthold HJ, O’Meara E et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. *Int J Radiat Oncol Biol Phys* 2012;83:e353–62.

16. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354–60.

17. Chen MF, Tseng CJ, Tseng CC et al. Clinical outcome in post-hysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438–44.

18. Folkert MR, Shih KK, Abu-Rustum NR et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. *Gynecol Oncol* 2013;128:288–93.

19. Isohashi F, Mabuchi S, Yoshioka Y et al. Intensity-modulated radiation therapy versus three-dimensional conformal radiation therapy with concurrent nedaplatin-based chemotherapy after radical hysterectomy for uterine cervical cancer: comparison of outcomes, complications, and dose–volume histogram parameters. *Radiat Oncol* 2015;10:180.

20. Suresh UR, Smith VJ, Lupton EW et al. Radiation disease of the urinary tract: histological features of 18 cases. *J Clin Pathol* 1993;46:228–31.

21. Hazewinkel MH, Sprangers MA, van der Velden J et al. Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. *Gynecol Oncol* 2010;117:281–6.

22. Isohashi F, Yoshioka Y, Mabuchi S et al. Dose–volume histogram predictors of chronic gastrointestinal complications after radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. *Int J Radiat Oncol Biol Phys* 2013;85:728–34.

23. Chopra S, Dora T, Chinnachamy AN et al. Predictors of grade 3 or higher late bowel toxicity in patients undergoing pelvic radiation for cervical cancer: results from a prospective study. *Int J Radiat Oncol Biol Phys* 2014;88:630–5.

24. Kavanagh BD, Pan CC, Dawson LA et al. Radiation dose–volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76:S101–7.