CT-based 3D Dose-Volume Parameter of the Rectum and Late Rectal Complication in Patients with Cervical Cancer Treated with High-Dose-Rate Intracavitary Brachytherapy

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This study evaluated the efficacy of computed tomography (CT)-based three-dimensional (3D) dose-volume parameters of the rectum as predictor for late rectal complication (LRC) in cervical cancer patients treated with radiotherapy alone. Eighty-four patients treated with a combination of external radiotherapy and high-dose-rate intracavitary brachytherapy between January 2000 and December 2004 were retrospectively analyzed. Brachytherapy was prescribed with standard 2D planning. Patients underwent pelvic CT at brachytherapy. The external rectal wall was contoured on the CT images, and the minimum doses delivered to 0.1cc, 1cc, and 2cc of the most irradiated rectal volumes were calculated with dose-volume histograms. The International Commission of Radiation Units and Measurements (ICRU) rectal point dose was also calculated by conventional method. Total dose (external radiotherapy plus brachytherapy) to the rectum was transformed to the biologically equivalent dose in 2-Gy fractions with $\alpha/\beta$ of 3 Gy ($D_{0.1cc}$, $D_{1cc}$, $D_{2cc}$ and $D_{ICRU}$). The relationships between these dosimetric parameters and the incidence of LRC were analyzed. The 5-year overall actuarial rate of LRC was 26.4%. The values of $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ were significantly higher in patients with LRC than in those without (p < 0.001), but the difference in the values of $D_{ICRU}$ was not statistically significant (p = 0.10). The rate of LRC increased significantly with increasing $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ (p = 0.001). However, no positive dose-response relationship was observed between $D_{ICRU}$ and the rate of LRC (p = 0.42). The present study has suggested that CT-based 3D dose-volume parameters of the rectum may be effective for predicting LRC.

INTRODUCTION

Intracavitary brachytherapy (ICBT) is an important treatment modality for carcinoma of the uterine cervix. Because this treatment is characterized by a steep dose gradient, it can deliver a high dose to the cervical tumor while minimizing doses to the surrounding normal tissues. In some cases, however, the rectum, sigmoid colon, and/or bladder are irradiated with high doses because of close proximity to the cervical tumor, and this may result in late radiation complications.1,2) Late rectal complication (LRC) is one of the most important dose-limiting toxicities, as severe LRC, such as a rectal ulcer or fistula, can be life-threatening. To assess the rectal dose of ICBT, X-ray-based two-dimensional (2D) treatment planning has traditionally been performed, and the International Commission on Radiation Units and Measurements (ICRU) rectal reference point has been used as the standard dose-specific point.3) Several investigators reported a positive correlation between the ICRU rectal point dose and the occurrence of LRC by the treatment of either low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy.4–7) However, several other investigators could not find a positive correlation between them.8–10) Because the ICRU rectal point is
hypothesised point determined by the two orthogonal X-rays, it may not always represent the exact location of the highest dose in the rectum.11,12)

Recently, computed tomography (CT) and magnetic resonance imaging (MRI) have increasingly been used for treatment planning of ICBT for cervical cancer, as these imaging modalities provide more accurate information than orthogonal X-rays on the topographic relationship between applicators, the cervical tumor and organs at risk (OARs). Treatment planning using CT or MRI images also allows assessment of three-dimensional (3D) dose distributions and dose-volume evaluation for tumor and OARs. The Group Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) working group for gynecologic brachytherapy has provided recommendations on 3D image-based treatment planning in cervical cancer brachytherapy.13,14) To assess the rectal dose by ICBT, 3D dose-volume parameters, including the minimum doses delivered to 0.1cc, 1cc, and 2cc of the most irradiated rectal volume, are recommended for recording and reporting. Several authors have reported that 3D image-based brachytherapy, according to the GEC-ESTRO recommendations, could improve target volume coverage and reduce doses to OARs.15,16) However, only a few reports have been published on the relationship between the 3D dose-volume parameters and clinical outcomes.17-20) Especially, dose-response relationships between the 3D dose-volume parameters of the rectum and LRC have not been thoroughly evaluated clinically.

Since a CT scanner was installed in the ICBT treatment room of our hospital in 2000, we have been taking pelvic CT images at ICBT with the applicators in place. After treatment, almost all patients underwent long-term follow-up, and clinical data on disease status, early and late radiation complications, quality of life, and life and death were recorded. We have already reported a positive correlation between the maximum rectal dose calculated by CT images and the incidence of LRC.21) In the present study, we analyzed the relationship between CT-based 3D dose-volume parameters of the rectum and the incidence of LRC. The objective of this study was to evaluate the efficacy of the dose-volume parameters as predictor for LRC in cervical cancer patients treated with definitive radiotherapy.

METHODS AND MATERIALS

Patients
Eighty-four patients treated with radiotherapy alone between January 2000 and December 2004 were retrospectively analyzed. As the pure radiation dose-volume effect to the rectum was investigated in the present study, patients treated with chemoradiotherapy were excluded. All patients (median age 69 years, range 30–86) had previously untreated cervical cancer, and according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, 19 patients had Stage IB, 37 had Stage II, 20 had Stage III, and 8 had Stage IVA disease. Histologically, 79 patients had squamous cell carcinoma and 5 had adenocarcinoma or adenosquamous carcinoma. All patients underwent CT of the abdomen and pelvis and MRI of the pelvis before treatment. Cervical tumor dimensions were measured based on T2-weighted MRI images. Forty-six patients had tumors < 4 cm and 38 had tumors ≥ 4 cm in maximum diameter.

Radiotherapy
Patients were treated with a combination of external beam radiotherapy (EBRT) and HDR-ICBT according to the Japanese treatment guidelines.22) EBRT was delivered to the whole pelvis through anterior and posterior parallel-opposed portals using 10-MV X-rays with a daily fraction dose of 1.8 or 2.0 Gy. The median total dose delivered to the pelvic sidewall was 50 Gy (range, 36–60.6 Gy). In principle, a central shield (3–4 cm width at the isocenter) was inserted into the treatment field after delivering 19.8 Gy to the whole pelvis in patients with early-stage disease (stage I–II and tumor size ≤ 4 cm in maximum diameter). In patients with advanced-stage disease (stage III–IVA or tumor size > 4 cm in maximum diameter), a central shield was usually inserted after 30.6 Gy of whole pelvic irradiation.

HDR-ICBT was performed using the 192Ir remote after-loading system (microSelectron, Nucletron, Veenendaal, The Netherlands). A combination of tandem and ovoid applicators was used for most patients. A combination of tandem and vaginal cylinder was used for some patients with narrow vagina or those with tumor infiltration to the lower vagina. A foley catheter was inserted and balloonied with 7 ml of contrast medium to localize the bladder neck. The bladder was filled with 100 ml of normal saline to avoid high-dose irradiation to the whole volume of the bladder. Bowel preparation was performed to achieve an empty rectum and sigma. After implantation of the applicators, two orthogonal X-rays were taken, and standard 2D treatment planning was performed using the treatment planning system (Plato BPS, version 13.7, Nucletron, Veenendaal, The Netherlands). HDR-ICBT was performed once a week, concurrently with central-shielding EBRT. The median total point A dose of ICBT was 24 Gy in 4 fractions (range, 10–30 Gy).

3D dosimetry
Both a C-arm type X-ray unit and a CT scanner were installed in the treatment room. All patients underwent plain pelvic CT at brachytherapy with the applicators in place. After taking orthogonal radiographs, CT images with 5-mm slice thickness were taken in the same supine position on the same treatment couch. All CT images were electrically stored.

The contour of the rectum was determined by two radiation oncologists (S. K. and T. L.). According to the GEC-ESTRO recommendations,13) the external rectal wall was delineated on the CT images using Oncentra Masterplan
(Nucletron). The contour of the rectum began at the anorectal junction and ended at the rectosigmoid flexure. For precise contour delineation, MRI and CT images at diagnosis were always referred to.

The CT data sets were imported into the treatment planning system (Plato BPS). The dose distribution generated by X-ray-based 2D planning was superimposed on the CT data set by matching the applicator positions (Fig. 1). A cumulative dose-volume histogram (DVH) of the rectum was calculated, and the minimum doses delivered to 0.1cc, 1cc, and 2cc of the most irradiated rectal volume were derived from the DVH according to the GEC-ESTRO recommendation.14) Many patients could undergo CT scans at the first session of ICBT only. Therefore, the cumulative dose to the rectum for all ICBT fractions was calculated by multiplying the corresponding dose by the fraction number of ICBT as the most practical method. Regarding the rectal dose from EBRT, it was assumed that the whole rectum received 100% of the prescribed EBRT dose before central shield.

When applying 3D dose volume assessments, the doses to the rectum from both EBRT and ICBT were normalized to the biologically equivalent doses in 2 Gy fractions (GyEQD2) based on the linear-quadratic model using an α/β ratio of 3 Gy. 3D dose-volume parameters of the rectum (D0.1cc, D1cc, and D2cc) were calculated by adding the biologically equivalent doses of whole pelvic EBRT and all ICBT fractions. The dose at the ICRU rectal point was calculated in each ICBT session by conventional method, and the total dose at the ICRU rectal point was calculated with the same way (DICRU).

Assessment of late rectal complications

After treatment, patients were followed up monthly in the first year, bi-monthly in the second year, and every 3–4 months in the third to fifth years. Follow-up evaluation consisted of history-taking, physical examination, and routine blood tests. CT of the abdomen and pelvis and/or MRI of the pelvis were performed once or twice a year for most patients. Stool examination was indicated when LRC was suspected. Late rectal complications were graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization of Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme.23)

![Fig. 1. Dose distributions of intracavitary brachytherapy projected onto the axial CT image.](image)

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![Fig. 2. Overall actuarial rate of late rectal complications.](image)

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| Table 1. Comparison of the values of dosimetric parameters between patients with and without late rectal complications (all Grades). |
|----------------------------------------|----------------|----------------||----------------|----------------|----------------|
| parameter | LRC (−) n = 64 | average (range) (GyEQD2) | LRC (+) n = 20 | average (range) (GyEQD2) | p value |
| DICRU | 73.9 (11.5–125.8) | 83.4 (43.5–127.8) | p = 0.10 |
| D0.1cc | 77.3 (15.0–157.2) | 111.4 (54.8–156.1) | p < 0.001 |
| D1cc | 61.7 (13.2–115.8) | 85.4 (51.0–136.9) | p < 0.001 |
| D2cc | 53.9 (12.1–93.0) | 72.0 (44.1–99.3) | p < 0.001 |

Abbreviations: LRC, late rectal complication; EQD2, biologically equivalent dose in 2-Gy fractions; ICRU, International Commission on Radiation Units and Measurements.

| Table 2. Comparison of the values of dosimetric parameters between patients with and without Grade 2 late rectal complications. |
|----------------------------------------|----------------|----------------||----------------|----------------|----------------|
| parameter | LRC (−) n = 77 | average (range) (GyEQD2) | LRC (+) n = 7 | average (range) (GyEQD2) | p value |
| DICRU | 74.8 (11.5–125.8) | 90.9 (46.7–127.8) | p = 0.07 |
| D0.1cc | 83.8 (15.0–157.2) | 104.1 (71.3–152.6) | P = 0.12 |
| D1cc | 66.2 (13.2–136.9) | 80.1 (65.8–119.5) | P = 0.12 |
| D2cc | 57.2 (12.1–93.0) | 69.3 (56.2–95.3) | P = 0.08 |

Abbreviations: LRC, late rectal complication; EQD2, biologically equivalent dose in 2-Gy fractions; ICRU, International Commission on Radiation Units and Measurements.
**Statistical analysis**

The two-sided paired t-test was used to compare the distribution of the dosimetric parameters between patients with and without LRC. The overall actuarial rate of LRC was calculated using the Kaplan-Meier method. The time to LRC was measured from the date of radiotherapy initiation to the date of the first episode of LRC. Patients who died without complications were censored at the time of death, and surviving patients without complications were also censored at the date of their last follow-up. To analyze the dose-response relationship, patients were classified into several groups according to their values of dosimetric parameters, and the 5-year LRC rates for the respective groups were compared. The log-rank test was used for comparison. A p-value ≤ 0.05 was considered to indicate a statistically significant difference.

**RESULTS**

The median follow-up duration for all patients was 43.9 months (12 to 91 months). The 5-year overall survival and local control rates for all patients were 77.7% and 90.4%, respectively. Twenty (23.8%) patients developed LRC, 13 with Grade 1 and 7 with Grade 2. No severe (Grades 3–5) complication was observed. The 5-year actuarial rate of LRC was 26.4% (Fig. 2).

The values of $D_{0.1cc}$, $D_{1cc}$, $D_{2cc}$, and $D_{ICRU}$ for patients with and without LRC are summarized in Table 1. The values of $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ were significantly higher in patients with LRC than in those without ($p < 0.001$). Although the values of $D_{ICRU}$ tended to be higher in patients with than without LRC, the difference between the two groups was not significant ($p = 0.10$). When the values of these dosimetric parameters were compared between patients with and without Grade 2 LRC, no statistically significant difference was observed (Table 2).

For dose-response relationship analysis, patients were classified into six groups with their values of dosimetric parameters by 10-Gy EQD2 ($D_{1cc}$, $D_{2cc}$, and $D_{ICRU}$) or 20-Gy EQD2 ($D_{0.1cc}$) increments. The actuarial rates of LRC for patients in the respective groups are shown in Fig. 3A–D. The LRC rate significantly increased with increasing $D_{0.1cc}$ ($p = 0.001$), $D_{1cc}$ ($p = 0.001$), and $D_{2cc}$ ($p = 0.001$). However, no positive dose-response relationship was observed between $D_{ICRU}$ and the rate of LRC ($p = 0.42$).

**DISCUSSION**

In the treatment planning for cervical cancer brachytherapy, MRI- or CT-based 3D treatment planning is being increasingly used these days. To assess the dose to the rectum, 3D dose-volume parameters, including $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ of the rectum calculated with DVH, are recommended for recording and reporting. Several investigators reported the relationship between these 3D dose-volume parameters and clinical outcomes. Georg et al. calculated MRI-based dose-volume parameters and analyzed their correlation with clinical symptoms and rectosigmoidoscopic findings. They reported that $D_{2cc}$ was significantly higher in patients with...
clinical symptoms or moderate to severe mucosal changes than in those without. Koom et al. compared CT-based dose-volume parameters with the findings of rectosigmoidoscopy, reporting that $D_{0.1cc-2cc}$ were significantly greater in patients with moderate to severe mucosal changes. These data suggested that 3D dose-volume parameters may possess good predictive value for LRC. However, long-term follow-up data on dose-volume parameters are quite limited, and therefore the predictive value for LRC has still to be established.

In the present study, we calculated $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ of the rectum using CT images according to the GEC-ESTRO recommendations and compared them with the incidence of LRC. To the best of our knowledge, this is the first study to analyze the relationship between 3D dose-volume parameters and the long-term incidence of LRC. Consequently, positive dose-response relationships were observed between $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ of the rectum and the incidence of LRC (Table 1, Fig. 3A–C). From the results, it was suggested that CT-based 3D dose-volume parameters of the rectum might be effective indicators for predicting LRC.

In the present study, however, no positive dose-response relationship was observed between $D_{0.1cc}$, $D_{1cc}$, and $D_{2cc}$ and Grade 2 LRC, probably because of the small number of patients developing Grade 2 LRC (Table 2). Furthermore, it was not possible to examine the relationship between dose-volume parameters and severe LRC, as Grade 3–5 LRC was not seen in the study. Regarding the relationship between 3D dose-volume parameters and severe LRC, there have only been a few reports in the literature. Potter et al. treated cervical cancer patients with MRI-based HDR-ICBT and reported a low rate of LRC (Grade 1–2, 4%; Grade 3–4, 0%). $D_{2cc}$ of the rectum was limited to 75–78 Gy$_{EQD2}$ in their series, and they suggested that the dose constraint had contributed to the low rate of LRC. However, this dose constraint was based on clinical data from the relationship between the ICRU rectal point dose and moderate or severe LRC. Therefore, further study is needed to evaluate the dose-response relationship between 3D dose-volume parameters and severe LRC and to determine the threshold dose for severe LRC.

Regarding the relationship between the ICRU rectal point dose and the incidence of LRC, several reports have demonstrated either positive or negative correlation between them. In the present study, no significantly positive relationship was observed between $D_{ICRU}$ and the incidence of LRC, although the values of $D_{ICRU}$ tended to be higher in patients with than without LRC (Table 1, Fig. 3D). The dose distributions projected onto CT images demonstrated that, in some patients, the ICRU rectal point was not the exact location in the rectum receiving the highest dose. In these cases, the rectum was found to have shifted laterally, or the dose distributions were not symmetrical because of non-ideal applicator geometry. Several studies demonstrated either positive or negative correlation between 3D dose-volume parameters and the ICRU rectal dose, and this discrepancy might be explained by geometrical variations between applicators and rectum. From these results, it was suggested that the ICRU rectal point dose might not always be a good predictor for LRC.

To calculate the rectal dose from EBRT, it was assumed that the whole rectum received 100% of the prescribed EBRT dose before central shield in the present study. However, inhomogeneity exists in EBRT dose distribution, even when anterior and posterior parallel-opposed portals or four-field box technique is used. Generally speaking, this dose inhomogeneity is not larger than $\pm 5\%$ for the dose of EBRT, which is much smaller compared with that of ICBT. Therefore, according to the GEC-ESTRO recommendation, it should be assumed that a homogeneous dose is delivered to the rectum at EBRT.

It was also assumed in the present study that the rectum was completely shielded from EBRT after inserting the midline block. However, the rectum might be irradiated with some doses after central shield by the topographic relationship between the midline block and the rectum. But the rectal wall receiving a high dose at ICBT is always adjacent to the applicator. And it can be shielded from EBRT by the midline block unless the applicator position is shifted extremely laterally. Therefore, the possibility of receiving some EBRT doses after central shield is not considered to be of great concern in calculating $D_{0.1cc-2cc}$ of the rectum.

In assessing the doses to OARs, the GEC-ESTRO working group also recommends $D_{5cc}$ and $D_{10cc}$, if contouring organ walls is performed. Strictly speaking, the doses to the organ walls should be calculated in the assessment of late complications. However, it is generally difficult to manually delineate very small organ walls, especially the walls of the rectum and sigmoid colon. It is also difficult to have automatically generated second contours at selected distances by the current treatment planning system. When volumes smaller than 5cc are considered, the DVHs based on organ contour and organ wall contour can lead to almost identical numerical results. Therefore, it is considered the practical way to calculate $D_{0.1cc-2cc}$ of the rectum from organ contouring only.

Although MRI is superior to CT in visualizing cervical tumors, we used CT rather than MRI images because, as in many other institutions, the MRI unit is located far from the brachytherapy room. As for brachytherapy applicators, we have never used MRI-compatible non-metallic applicators, but we have used thin metallic tandem and ovoid applicators without tungsten shields. These applicators are less expensive than the MRI-compatible ones and can produce acceptable CT images with minimum image artifacts for contouring target volumes and OARs. Several investigators have described that the outer walls of the bladder and rectum were clearly visualized on CT images, although they had
some limitations in visualizing the cervical tumor and its extent.\textsuperscript{13,28} Also in the present study, the external rectal walls were clearly visualized on CT images in most cases. Therefore, CT images are considered to be adequate for the DVH analysis of the rectum.

CT images at brachytherapy were generated with 5-mm slice thickness in the present study. However, when using this slice thickness, two problems arose in the 3D treatment planning of ICBT. One was positional inaccuracy in reconstructing the applicator geometry, and the other was volumetric inaccuracy in contouring the intricately shaped organs. Because the active dwell positions may be shifted, added, or skipped by at least 2.5-mm steps to optimize dose distribution,\textsuperscript{15} we have now changed the imaging protocol and take CT images at 2.5-mm slice thickness.

In the present study, it was not feasible to perform CT scan at every ICBT session for several practical and logistical reasons. In fractionated ICBT, however, the doses to the bladder and rectum may change between fractions according to geometrical variations in the applicators and these organs. For accurate evaluation, it is preferable to perform 3D image-based treatment planning at every ICBT session.\textsuperscript{79,30} Therefore, there was a limitation to the accuracy of the dose-volume parameters in the present study. Despite this limitation, the 3D dose-volume parameters analyzed here showed positive correlations with the incidence of LRC, giving impetus to further study. We are now making every effort to perform CT-based treatment planning at every ICBT session.

In conclusion, CT-based 3D dose-volume parameters of the rectum according to the GEC-ESTRO recommendations may represent effective predictors for LRC. Further study is needed to evaluate the dose-response relationship between 3D dose-volume parameters and severe LRC and to determine the threshold dose for severe LRC.

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REFERENCES


