A retrospective comparison of outcome and toxicity of preoperative image-guided intensity-modulated radiotherapy versus conventional pelvic radiotherapy for locally advanced rectal carcinoma

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ABSTRACT

The aim of the study was to compare clinical outcomes and toxicity between 3D conformal radiotherapy (3DCRT) and image-guided intensity-modulated radiotherapy (IG-IMRT) administered through helical tomotherapy in locally advanced rectal cancer (LARC) patients receiving preoperative chemoradiotherapy. We reviewed 144 patients with Stage II–III rectal cancer receiving preoperative fluoropyrimidine-based chemoradiotherapy followed by radical resection. Tumor responses following chemoradiotherapy were evaluated using the Dworak tumor regression grade (TRG). Of the 144 patients, 45 received IG-IMRT and 99 received 3DCRT. A significant reduction in Grade 3 or 4 acute gastrointestinal toxicity (IG-IMRT, 6.7%; 3DCRT, 15.1%; \( P = 0.039 \)) was observed by IG-IMRT. The pathologic complete response (pCR) rate did not differ between the IG-IMRT and the 3DCRT group (17.8% vs 15.1%, \( P = 0.52 \)). Patients in the IG-IMRT group had the trend of favorable tumor regressions (TRG 3 or 4) compared with those in the 3DCRT group (66.7% vs 43.5%, \( P = 0.071 \)). The median follow-up was 53 months (range, 18–95 months) in the 3DCRT group and 43 months (range, 17–69 months) in the IG-IMRT group. Four-year overall, disease-free, and local failure–free survival rates of the IG-IMRT and 3DCRT groups were 81.6% and 67.9% (\( P = 0.12 \)), 53.8% and 51.8% (\( P = 0.46 \)), and 74.6% and 55.9% (\( P = 0.06 \)), respectively.
(\(P = 0.51\)), and 88% and 75.1% (\(P = 0.031\)), respectively. LARC patients treated with preoperative IG-IMRT achieved lower acute gastrointestinal adverse effects and a higher local control rate than those treated with 3DCRT, but there was no prominent difference in distant metastasis rate and overall survival between two treatment modalities.

**KEYWORDS:** image guidance, locally advanced rectal cancer, tomotherapy, conformal, toxicity, chemoradiotherapy

**INTRODUCTION**

Preoperative concurrent chemoradiotherapy (CCRT) followed by radical resection is currently the standard treatment for locally advanced rectal cancer (LARC) [1–3]. Although CCRT improves local control, the multimodality therapy contributes to several treatment-related toxic events. Of the numerous toxicities, some adverse events have been attributed to radiotherapy (RT) [4–6].

With advances in RT, high conformal radiation coverage of the target volumes with sparing of the surrounding normal tissues can be achieved through intensity-modulated radiotherapy (IMRT). Moreover, with the integration of image-guided radiotherapy (IGRT) and IMRT, a small planning target volume (PTV) margin can be applied, consequently further reducing potential radiation toxicity. Numerous dosimetric studies have reported that in pelvic malignancy irradiation, radiation to the small bowel, bladder, and rectum is lower in IMRT than in 3D conformal radiotherapy (3DCRT) [7–11]. However, few studies have compared the clinical outcomes directly between image-guided IMRT (IG-IMRT) and 3DCRT in LARC patients receiving preoperative CCRT. Therefore, we retrospectively analyzed the clinical outcomes and toxicities between IG-IMRT and 3DCRT in LARC patients at a single institution.

**MATERIALS AND METHODS**

**Patients**

We retrospectively reviewed the medical records of LARC patients treated with preoperative CCRT followed by radical resection between May 2006 and January 2015. The inclusion criteria were as follows: (i) pathologically proven rectal adenocarcinoma, (ii) locally advanced diseases (clinical T3–4 or nodal involvement), (iii) tumors located within 15 cm of the anal verge, (iv) patients receiving preoperative CCRT followed by intentional radical resection, and (v) no evidence of distant metastasis at diagnosis. The exclusion criteria were local excision of tumor, history of prior pelvic irradiation, and history of malignancies other than rectal cancer. The study was approved by the institutional ethics committee of our hospital.

Pretreatment evaluation entailed a complete history review and physical examination, colonoscopy, tumor biopsy, chest radiography, abdominal computed tomography (CT) and pelvic magnetic resonance imaging, serum carcinoembryonic antigen (CEA) level assessment, and routine laboratory studies. The tumor stage was classified according to the seventh edition of the AJCC Cancer Staging Manual and Handbook [12].

**RT technique**

All patients received planning CT in the supine position after they were immobilized using custom thermoplastic immobilization devices. All patients were asked to void and then drink 200 ml of water 30 min before CT simulation and each treatment. 3DCRT was delivered using the 2100 C/D linear accelerator (Varian Medical system, Palo Alto, CA). For the 3DCRT plan, a three-field technique included two opposed lateral fields and one posterior–anterior field with wedges and photon energy of 10 MV was used. RT was administered to the whole pelvis at a dose of 45 Gy in 25 fractions. Radiation portal fields were determined using the following rules: (i) superior border: L5–S1 interspace, (ii) inferior border: 3–4 cm below the primary tumor, (iii) lateral border: 1.5 cm outside the true bony pelvis, (iv) posterior margin: 1.5 cm behind the anterior bony sacral margin, and (v) anterior border: posterior border of the symphysis pubis.

IG-IMRT was administered using a Hi-Art system (TomoTherapy Inc., Madison, WI). A fixed-jaw mode with a field width of 2.5 or 5 cm was used for treatment planning, depending on overall treatment time. Pitch varied from 0.215 to 0.287. The modulation factor ranged from 2 to 3, depending on homogeneity and conformity index. The gross tumor volume was defined as rectal tumors and clustered lymph nodes or lymph nodes with diameter >1 cm. The clinical target volume (CTV<sub>45 Gy</sub>) included the primary tumor, the mesorectum, the sacral canal, and the following lymph nodes: perirectal, presacral, hypogastric, obturator, and internal iliac. If the tumor had invaded the prostate gland, bladder, or vagina, the CTV<sub>45 Gy</sub> was extended to cover the involved organ and the external iliac nodal regions. For lesions with anal invasion, the perineum and bilateral inguinal lymph nodes were included in the CTV<sub>45 Gy</sub>. A total dose of 45 Gy in 25 fractions was delivered to the planning target volume (PTV<sub>45 Gy</sub>) with a simultaneous integrated boost of 0.2 Gy per day for the primary tumor up to a total dose of 50 Gy. PTV with a superior, inferior, and radical margin of 5–7 mm was added to the CTV<sub>45 Gy</sub>. A more conservative PTV margin of 3 mm was added to the CTV<sub>50 Gy</sub> as a boost to the primary tumor. The treatment plan was accepted if \(>95\%\) of the PTV received the prescribed dose. The objective of sparing normal tissue was to reduce the volume of the small bowel irradiated with doses \(>15\) Gy and to maintain mean bladder doses at \(<21\) Gy. The bowel volume included individual bowel loops extending to 1.5 cm above the field edge. Before each treatment, patients were repositioned according to daily image guidance through megavoltage CT, which was coregistered with planning kilovoltage CT.

**Chemotherapy and surgery**

Concomitant with RT, chemotherapy, including bolus infusional 5-fluorouracil (5-FU) at 350 mg/m² during the first and fifth weeks...
of radiotherapy or capecitabine at 850 mg/m² twice daily for 5 days/week during the radiotherapy, was administered. Patients underwent total mesorectal excision (TME) 6–8 weeks after CCRT completion. Patients were recommended to receive adjuvant chemotherapy if they had one of the following risk factors: (i) pathologic lymph node metastasis, (ii) positive resection or circumferential margin, or (iii) pathologic T3–4 lesion [13]. Adjuvant 5-FU–based chemotherapy consisted of one of the following two regimens: (i) four cycles of monthly bolus injections of 5-FU (350 mg/m²/day) on Day 1–5; or (ii) six cycles of capecitabine 850 mg/m² twice daily for 14 days, followed by 7 days rest after each cycle.

Pathology review
Two experienced pathologists analyzed all resected specimens, using the standard method. The pathologic stage (ypT and ypN), histologic grade, lymphovascular invasion, perineural invasion, circumferential resection margin status, and tumor regression grade were documented. The tumor response following chemoradiotherapy was evaluated according to the Dworak tumor regression grade (TRG) [14]. Responders were defined as patients with a TRG of 3 or 4 and non-responders as those with a TRG of 0–2.

Toxicity evaluation
Acute toxicity was evaluated weekly according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep. cancer.gov/reporting/ctc.html). Late toxicity was graded according to the objective criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale, depending on the late adverse effects of RT [15].

Statistical analysis
The continuous parameters were represented as the median and range, while frequency and percentage were given for the categorical variables. The Chi-square test and the paired t test were used for comparison of categorical and continuous variables, respectively. Survival times were estimated using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards model was used to evaluate the association between clinical parameters and survival using the backward stepwise procedure. Data analyses were performed using the JMP software (version 9.0, SAS Institute Inc., Cary, NC). Results were considered significant at P < 0.05.

RESULTS
Patient demographics
The medical files of 172 LARC patients undergoing CCRT were retrieved for an initial analysis between May 2006 and January 2015. Of the 172 patients, 7 were lost to follow-up, 10 presented evidence of distant metastases at the initial diagnosis, 5 refused to undergo radical resection, and 6 received RT because of recurrent rectal cancer; these patients were excluded. Thus, 144 patients were enrolled into our study. Among the 144 patients in the current study, 45 patients received IG-IMRT and 99 patients received 3DCRT. The patient characteristics by treatment group are summarized in Table 1. No significant differences were observed between the IG-IMRT and 3DCRT groups.

Dose–volume histogram and acute toxicity
Table 2 presents the dose–volume histogram data between the two treatment groups. IG-IMRT significantly decreased the high dose to the small bowel and the mean bladder dose compared with 3DCRT. Acute and late toxicities are summarized in Table 3. Only one patient experienced Grade 4 toxicity in the study. In Grade 3 or 4 (Grade 3+) overall acute toxicities, IG-IMRT resulted in significantly less overall Grade 3+ toxicity than 3DCRT (8.9% vs 20.2%, P = 0.042). The decreased incidence of Grade 3 or 4 acute gastrointestinal (GI) toxicity in the IG-IMRT group contributed to this reduction in overall Grade 3+ toxicity (6.7% vs 15.1%; P = 0.039). Of the three patients experiencing Grade 3 acute GI toxicity in the IG-IMRT group, two had diarrhea and one patient had proctitis. Of the 15 patients experiencing Grade 3+ acute GI toxicity in the 3DCRT group, 9 had diarrhea, 5 had proctitis, and 1 had nausea. The two treatment groups did not differ significantly in Grade 3+ acute hematologic and genitourinary (GU) toxicity.

All but two patients completed the planned radiation regimen in the current study, and those two patients were treated with 3DCRT. The RT course of one patient in the IG-IMRT group was interrupted because of Grade 3 diarrhea, and the RT course of eight patients in the 3DCRT group was interrupted: five for Grade 3 diarrhea, two for Grade 3 dermatitis, and one for Grade 3 leukopenia. The median RT duration was significantly shorter in the IG-IMRT group compared with that in the 3DCRT group (35 days vs 40 days, P = 0.016).

Post-operative complication and late toxicity
Among patients receiving low anterior resection, 2 of the 39 patients (5.1%) in the IM-IGRT group and 7 of the 86 patients (8.1%) in the 3DCRT group had anastomotic leakage. Of these patients, one in the IG-IMRT group and three in the 3DCRT group had pelvic abscess requiring percutaneous CT-guided drainage. All patients recovered uneventfully after medical or surgical treatments. No treatment-related deaths were reported.

Grade 3 or higher late GI toxicity was reduced in the IG-IMRT group (4.4%) versus in the 3DCRT group (10.1%), but this did not reach statistical significance (P = 0.071; Table 3). In the IG-IMRT group, one patient with Grade 3 small bowel obstruction 18 months after operation underwent surgical resection. Surgical intervention was performed on one patient who developed a colovaginal fistula 11 months postoperatively. No patient in the IG-IMRT group experienced Grade 3 or 4 late GU toxicity. In the 3DCRT group, five patients had Grade 3 small bowel obstructions, which were observed 12, 16, 21, 25 and 26 months after operation, respectively. Two patients had a Grade 3 anastomotic stenosis 11 and 19 months postoperatively. Grade 3 colitis was observed in two patients 13 and 22 months postoperatively. Two patients in the 3DCRT group had Grade 3 ureter strictures with symptomatic hydronephrosis requiring long-term double J catheter insertion; one had ureter stricture 20 months
Table 1. Patient characteristics in IG-IMRT and 3DCRT groups

| Characteristics                                      | IG-IMRT        | 3DCRT         | P       |
|------------------------------------------------------|----------------|---------------|---------|
| Age, median, year (range)                            | 64 (37–87)     | 61 (34–85)    | 0.183   |
| Gender                                               |                |               | 0.189   |
| Female                                               | 23 (51.1)      | 39 (39.4)     |         |
| Male                                                 | 22 (48.9)      | 60 (60.6)     |         |
| Clinical tumor depth                                 |                |               | 0.118   |
| T2                                                   | 5 (11.1)       | 9 (9.1)       |         |
| T3                                                   | 35 (77.8)      | 74 (74.7)     |         |
| T4                                                   | 5 (11.1)       | 16 (16.2)     |         |
| Clinical lymph node metastasis                       |                |               | 0.731   |
| N0                                                   | 12 (26.6)      | 22 (22.2)     |         |
| N1                                                   | 19 (42.2)      | 40 (40.4)     |         |
| N2                                                   | 14 (31.2)      | 37 (37.4)     |         |
| Distance from anal verge (cm)                        |                |               | 0.073   |
| <5                                                   | 32 (71.1)      | 55 (55.5)     |         |
| 5–10                                                 | 12 (26.7)      | 34 (34.3)     |         |
| 11–15                                                | 1 (2.2)        | 10 (10.2)     |         |
| Tumor differentiation                                |                |               | 0.524   |
| Well                                                 | 4 (8.8)        | 4 (4)         |         |
| Moderately                                           | 38 (84.4)      | 88 (88.9)     |         |
| Poorly                                               | 3 (6.8)        | 7 (7.1)       |         |
| Pretreatment CEA (ng/ml)                             |                |               | 0.745   |
| ≤5                                                   | 16 (35.6)      | 38 (38.4)     |         |
| >5                                                   | 29 (64.4)      | 61 (61.6)     |         |
| Concurrent chemotherapy                              |                |               | 0.093   |
| Infusion 5-FU                                        | 15 (33.3)      | 54 (54.5)     |         |
| Capecitabine                                         | 30 (66.7)      | 45 (45.5)     |         |
| Type of surgery                                      |                |               | 0.773   |
| Lower anterior resection                             | 39 (88.9)      | 86 (86.8)     |         |
| Abdominoperineal resection                           | 5 (11.1)       | 13 (13.2)     |         |
| Anal-preserving surgery (for low rectal tumor)       |                |               |         |
| Yes                                                  | 27 (84.4)      | 42 (76.4)     | 0.366   |
| No                                                   | 5 (15.6)       | 13 (23.6)     |         |
| Median RT dose, Gy (range)                           | 50 (45–50)     | 50.4 (41.4–50.4) | 0.692 |
| Adjuvant chemotherapy                                |                |               | 0.186   |
| Yes                                                  | 21 (46.7)      | 53 (53.5)     |         |
| No                                                   | 24 (53.3)      | 46 (46.5)     |         |
| Median follow-up, month (range)                      | 43 (17–69)     | 53 (18–95)    |         |

Data are presented as n (%), unless otherwise indicated. IG-IMRT = image-guided intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy, CEA = carcinoembryonic antigen, 5-FU = 5-fluorouracil, RT = radiotherapy.
Table 2. Dose–volume histogram data between IG-IMRT and 3DCRT

|                        | IG-IMRT | 3DCRT | P    |
|------------------------|---------|-------|------|
| GTV volume (cm³)       | 67 ± 59 | 72 ± 62 | 0.362|
| PTV volume (cm³)       | 799 ± 355 | 812 ± 383 | 0.428|
| SB volume (cm³)        | 611 ± 314 | 682 ± 364 | 0.246|
| Bladder volume (cm³)   | 162 ± 103 | 132 ± 98  | 0.193|
| V5-SB (cm³)            | 482 ± 244 | 372 ± 262 | 0.003|
| V10-SB (cm³)           | 392 ± 173 | 353 ± 218 | 0.089|
| V15-SB (cm³)           | 226 ± 99  | 255 ± 185 | 0.032|
| V20-SB (cm³)           | 97 ± 49   | 188 ± 126 | 0.012|
| V25-SB (cm³)           | 43 ± 26   | 176 ± 131 | 0.008|
| V30-SB (cm³)           | 18 ± 18   | 161 ± 118 | 0.002|
| V35-SB (cm³)           | 10 ± 14   | 157 ± 112 | 0.001|
| V40-SB (cm³)           | 4 ± 9     | 145 ± 120 | <0.001|
| V45-SB (cm³)           | 0.7 ± 2   | 137 ± 104 | <0.001|
| Mean bladder dose (Gy) | 18.6 ± 6  | 27.2 ± 14.9 | 0.015|
| V21-bladder (%)        | 36 ± 27   | 50 ± 36   | 0.023|

Data are presented as mean ± standard deviation. IG-IMRT = image-guided intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy, GTV = gross tumor volume, PTV = planning target volume, SB = small bowel, V dose = the percentage of the organ at least covered by each dose.

after surgery, and the other had the toxicity 27 months postoperatively. One patient had a Grade 3 rectovesical fistula 22 months postoperatively and required surgery.

**Surgery and pathologic response**

All patients completed TME. The median time from the end of RT to surgery was 7 weeks (range, 6–8 weeks). The median time interval between radiotherapy and surgery was no different between the IMRT group and the 3DCRT group (7 vs 7 weeks, P = 1.00). The pathologic characteristics are detailed in Table 4. There were more ypT3 and ypT4 patients in the 3DCRT group compared with in the IG-IMRT group (51.4% vs 40%, P = 0.22); however, the difference did not reach statistical significance. In addition, IG-IMRT resulted in favorable tumor regressions (TRG 3 or 4) compared with 3DCRT (66.7% vs 43.5%, P = 0.071). Downstaging of the T category from cT3–4 to ypT0–2 was observed in 24 (60%) and 53 (58.8%) patients in the IG-IMRT and 3DCRT groups, respectively (P = 0.91). Nodal downstaging from the clinically positive lymph node status to ypN0 was observed in 25 (75.7%) and 62 (79.4%) patients in the IG-IMRT and 3DCRT groups, respectively (P = 0.67). Of the 144 patients in this study, a pathologic complete response (pCR) was achieved in 23 patients (16%). The pCR rate did not differ between the IG-IMRT and 3DCRT groups (17.8% vs 15.1%, P = 0.53). In the 3DCRT group, 2 patients exhibited ypT0N1a and ypT0N1c, and neither of them developed recurrence after 2 years of follow-up.

**Failure patterns and survival data**

The median follow-up was 53 months (range, 18–95 months) in the 3DCRT group and 43 months (range, 17–69 months) in the IG-IMRT group. There were 5 patients in the IG-IMRT group who died; 4 deaths were due to tumor progressions and one died from a heart attack. In the 3DCRT groups, 22 patients died from recurrent tumors, 3 patients died from cardiovascular events and one patient had a fatal car accident. The most common site for local relapse was the presacral space (56.5%), followed by the anastomotic site (39.1%); however, there was no significant difference in local failure sites between the two treatment groups.

The 4-year overall survival (OS), disease-free survival (DFS), local failure–free survival (LFFS), and distant failure–free survival (DFFS) rates of patients in the IG-IMRT and 3DCRT groups were 81.6% and 67.9% (P = 0.12, Fig. 1A), 53.8% and 51.8% (P = 0.51, Fig. 1B), 88% and 75.1% (P = 0.031, Fig. 1C) and 65.4% and 62% (P = 0.61, Fig. 1D), respectively. Table 5 lists the Cox-proportional hazards analysis for LFFS. Multivariate analysis demonstrated use of IG-IMRT was an independent predictor of LFFS. The 4-year OS rates were 85.4% and 56.2% for responders and non-responders, respectively (P = 0.001, Fig. 1E). The 4-year DFS rates were 66.2% and 40.8% for responders and non-responders, respectively (P = 0.007, Fig. 1F).

**DISCUSSION**

Numerous dosimetric comparisons between IMRT and conventional RT techniques in rectal cancer patients have shown that IMRT entails higher target conformity and lower bowel and bladder exposure [7, 8, 16]. However, reports of clinical outcome and toxicity comparisons between IMRT and 3DCRT have rarely been published, particularly comparisons with IG-IMRT. Table 6 summarizes the efficacy and adverse effects of previously published studies of comparisons between IMRT and 3DCRT for rectal cancer patients. Four retrospective series compared the use of IMRT with 3DCRT [4, 5, 17, 18]. Droge et al. compared volumetric-modulated arc therapy (VMAT) with 3DCRT in patients homogeneously treated according to the CAO/ARO/AIO-04 trial and reported that VMAT reduced acute and late adverse effects [19]. However, the median follow-up time was 18.3 months in the VMAT group, which was too short to represent cumulative rates of late toxicity, and survival or disease control status comparisons between the VMAT and 3DCRT groups were not reported. To the best of our knowledge, this is the first comprehensive study comparing clinical outcomes and toxicities of IG-IMRT and 3DCRT with a longer follow-up time.

In our study, patients receiving IG-IMRT had significantly reduced severe acute GI toxicity compared with those receiving 3DCRT (6.7% vs 15.1%, P = 0.039). In our cohort, diarrhea was the
Table 3. Comparison of toxicity and treatment breaks in IG-IMRT and 3DCRT groups

|                     | IG-IMRT  
|---------------------|------------------------|
|                     |  
| Overall Grade 3 or 4 toxicity | 4 (8.9)   |
| Skin                | 96 (97.0)             |
| Grade 0–2           | 44 (97.8)             |
| Grade 3/4           | 1 (2.2)/0 (0)         |
| GI                  | 42 (93.3)             |
| Grade 0–2           | 84 (84.8)             |
| Grade 3/4           | 3 (6.7)/0 (0)         |
| GU                  | 45 (100)              |
| Grade 0–2           | 96 (97.0)             |
| Grade 3/4           | 0 (0)/0 (0)           |
| Hematological       | 45 (100)              |
| Grade 0–2           | 97 (98.9)             |
| Grade 3/4           | 0 (0)/0 (0)           |
| Treatment break     | 1 (2.2)               |
|                     | 8 (8.1)               |
| Postoperative       | 2 (5.1)               |
| complications       | 7 (8.1)               |
| Anastomotic leakage | 1 (2.5)               |
| Pelvic abscess      | 3 (3.5)               |
| Late toxicity       | 4 (8.9)               |
| Overall Grade 3 or 4 toxicity | 13 (13.1) |
| GI                  | 43 (95.6)             |
| Grade 1–2           | 89 (89.9)             |
| Grade 3/4           | 2 (4.4)/0 (0)         |
| GU                  | 45 (100)              |
| Overall Grade 3 or 4 toxicity | 96 (96.9) |
| GI                  | 0 (0)/0 (0)           |
| Grade 1–2           | 3 (3.1)/0 (0)         |
| Grade 3/4           | 0 (0)/0 (0)           |

Data are presented as n (%). IG-IMRT = image-guided intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy, GI = gastrointestinal, GU = genitourinary.

most common acute GI toxicity and the most common reason for RT interruption. Samuelian et al. retrospectively compared the acute toxicity of IMRT and 3DCRT in combination with chemotherapy in rectal cancer patients and reported that IMRT resulted in lower Grade ≥2 acute GI toxicity than did 3DCRT (32% vs 62%) [5]. Although the reduction in GI toxicity obtained using IMRT is consistent with our results, Samuelian et al. included patients with recurrent disease who received RT postoperatively and who were treated with non-curative intent, which might influence target delineation and the dosage of radiotherapy or chemotherapy and consequently the clinical outcome and toxicity. Parekh et al. retrospectively analyzed 48 rectal cancer patients receiving either IMRT- or 3DCRT-based preoperative chemoradiotherapy and reported a significant reduction in Grade ≥2 GI toxicity (30% vs 60.7%) [4]. Our results demonstrated that IG-IMRT significantly reduced Grade 2 and 3 GI toxicity. The possible reason for the reduced Grade 3 GI toxicity is
the combination of daily IGRT with IMRT in this study. In general, the incidence of Grade 3 diarrhea and proctitis in rectal cancer patients receiving conventional RT combined with 5-FU is 12–36%, which is considerably higher than observed in our current results. With reduced irradiated bowel volumes through the use of IMRT and minimized planning target margins through the use of IGRT, Grade 3 or 4 GI toxicity was lower than with 3DCRT. In addition, with the dynamic-jaw mode of tomotherapy, we may improve the longitudinal dose conformity, and we can reduce the penumbra superiorly and inferiorly to the target, resulting in less integral dose and toxicity. We did not use dynamic-jaw mode in the current study because the dynamic-jaw technique has only been available at our institute since September 2015. Further investigations on association between use of the dynamic-jaw mode and pelvic radiation-related toxicity are warranted.

In this study, treatment responders (TRG 3–4) had a higher OS and DFS than did the non-responders (TRG 0–2) (77.6% vs 52.2% and 61.7% vs 40.8%, respectively; Fig. 1E, F). Treatment response to neoadjuvant CCRT is an early indicator of the long-term prognosis in LARC patients [23, 24]. In the CAO/ARO/AIO-94 trial, patients with complete (TRG 4) or intermediate pathologic responses (TRG 2 and 3) had improved DFS after preoperative CCRT than those with poor responses [25]. Furthermore, Ark et al. analyzed 725 rectal cancer patients receiving neoadjuvant CCRT followed by radical resection and they demonstrated that tumor response (complete vs intermediate vs poor) was associated with 5-year recurrence-free survival, distant metastasis, and local recurrence rates [26]. The findings indicate that treatment response is closely correlated to the oncologic prognosis. In this study, patients receiving IG-IMRT had the trend of favorable tumor regressions compared with those receiving 3DCRT (66.7% vs 43.5%, P = 0.071). In addition, patients receiving IG-IMRT exhibited improved LFFS rates; however, no significant difference was

Table 4. Pathology characteristics in IG-IMRT and 3DCRT groups

| Characteristics                      | IG-IMRT | 3DCRT | P   |
|--------------------------------------|---------|-------|-----|
| Pathologic tumor depth               |         |       |     |
| ypT0                                 | 8 (17.8)| 17 (17.2)|     |
| ypT1                                 | 2 (4.4)| 5 (5.1)|     |
| ypT2                                 | 17 (37.8)| 26 (26.3)|     |
| ypT3                                 | 17 (37.8)| 44 (44.4)|     |
| pT4                                  | 1 (2.2)| 7 (7)|     |
| Pathologic lymph node metastasis     | 0.832   |       |     |
| pN0                                  | 34 (75.6)| 70 (70.7)|     |
| ypN1                                 | 8 (17.8)| 21 (21.2)|     |
| ypN2                                 | 3 (6.6)| 8 (8.1)|     |
| Pathologic complete response         | 0.527   |       |     |
| Median number of resected nodes       | 12 (0–21)| 10 (0–28)| 0.795^b |
| Median number of involved nodes       | 0 (0–9)| 0 (0–13)| 0.321^b |
| Tumor regression grade                | 0.092   |       |     |
| 0                                    | 1 (2.2)| 8 (8.1)|     |
| 1                                    | 6 (13.3)| 24 (24.2)|     |
| 2                                    | 8 (17.8)| 24 (24.2)|     |
| 3                                    | 22 (48.9)| 26 (26.3)|     |
| 4                                    | 8 (17.8)| 17 (17.2)|     |
| Treatment response                   | 0.071   |       |     |
| Favorable                            | 30 (66.7)| 43 (43.5)|     |
| Unfavorable                          | 15 (33.3)| 56 (56.5)|     |
| Surgical distal margin               | 0.383   |       |     |
| Negative                             | 42 (93.3)| 92 (92.9)|     |
| Positive                             | 3 (6.7)| 7 (7.1)|     |
| Circumferential resection margin     | 0.376   |       |     |
| Negative                             | 43 (95.6)| 96 (96.9)|     |
| Positive                             | 2 (4.4)| 3 (3.1)|     |
| Perineural invasion                  | 0.136   |       |     |
| Negative                             | 35 (77.8)| 65 (65.6)|     |
| Positive                             | 10 (22.2)| 34 (34.4)|     |

Table 4. Contd.

| Characteristics                      | IG-IMRT | 3DCRT | P   |
|--------------------------------------|---------|-------|-----|
| Lymphovascular invasion              | 0.699   |       |     |
| Negative                             | 38 (84.4)| 86 (86.8)|     |
| Positive                             | 7 (15.6)| 13 (13.2)|     |
| Tumor differentiation                | 0.823   |       |     |
| Well                                 | 6 (13.3)| 20 (20.2)|     |
| Moderately                           | 36 (80.0)| 77 (77.8)|     |
| Poorly                               | 3 (6.7)| 2 (2.0)|     |

Data are presented as n (%), unless otherwise indicated.

^Median (range).

^t-test.

*Favorable treatment responses included TRG 3 or 4; unfavorable treatment responses included TRG 0–2. IG-IMRT = image-guided intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy.
observed in OS and DFS between the treatment groups. This finding is consistent with other studies that suggest that RT usually contributes to improved locoregional control [1, 3].

In the present study, RT duration was shorter in the IG-IMRT group compared with that in the 3DCRT group (median time, 35 days vs 40 days). Prolonged RT duration has been associated with poor tumor responses. The CAO/AIO/ARO-94 trial demonstrated that prolonged radiation was correlated with higher locoregional recurrence [27]. Parekh et al. analyzed 48 LARC patients undergoing preoperative CCRT and showed that RT duration was significantly shorter in the IMRT group compared with that in the 3DCRT group. Moreover, patients receiving IMRT had favorable pathologic downstaging profiles [4]. In this study, patients requiring treatment interruptions were less in the IG-IMRT group compared with in the 3DCRT group. Therefore, a shorter RT duration in the IG-IMRT group may contribute to favorable tumor regressions.

Fig. 1. Comparison of the overall (A), disease-free (B), local failure-free (C), and distant failure-free (D) survival rates between the image-guided intensity-modulated radiotherapy (IG-IMRT) and 3D conformal radiotherapy (3DCRT) groups. The 4-year overall (E) and disease-free (F) survival rates for responders and non-responders.
Lymph node status is a significant prognostic factor in LARC patients undergoing neoadjuvant CCRT [28, 29]. Because the presacral space was the most common site of local failure in this study, we hypothesize that a higher boost dose to the presacral space might improve oncologic outcomes. Additional prospective randomized trials are required to verify this hypothesis.

Because IMRT enables us to gain steep dose gradients around target volumes, the potential for missing or underdosing tumors always raises concerns [30, 31]. Our study demonstrated the efficacy of T or N downstaging seemed to be similar between IG-IMRT and 3DCRT groups. We further evaluated those patients with locoregional recurrences and found that none of them were marginal failures. This implied that IMRT cooperated with IGRT would not compromise outcomes by potentially missing targets. However, further research is necessary to confirm the indications of IG-IMRT. Given the potential for marginal failures in rectal cancer.

### Table 5. Prognostic factor analysis for local-failure-free survival

| Variables                        | 4-year local-failure-free survival (%) | P value | Univariate | HR (95% CI; P) |
|----------------------------------|----------------------------------------|---------|------------|---------------|
| Type of radiotherapy             |                                        |         |            |               |
| IG-IMRT vs 3DCRT                 | 88 vs 75.1                             | 0.031   | 0.35 (0.11–0.94; 0.042) |
| Age (year)                       |                                        |         |            |               |
| ≤64 vs >64                       | 71.1 vs 82.6                           | 0.648   |            |               |
| Gender                           |                                        |         |            |               |
| Female vs male                   | 86.3 vs 73.5                           | 0.153   |            |               |
| Distance from anal verge (cm)    |                                        |         |            |               |
| ≤5 vs >5                         | 81.2 vs 76.4                           | 0.791   |            |               |
| Clinical tumor depth             |                                        |         |            |               |
| T2–3 vs T4                       | 85.6 vs 33.8                           | 0.001   | 0.15 (0.06–0.94; 0.012) |
| Clinical lymph node metastasis   |                                        |         |            |               |
| N0 vs N1–2                       | 81.8 vs 72.2                           | 0.128   |            |               |
| Type of chemotherapy             |                                        |         |            |               |
| 5-FU vs capecitabine             | 75.9 vs 82.7                           | 0.463   |            |               |
| Adjuvant chemotherapy            |                                        |         |            |               |
| Yes vs no                        | 83.5 vs 76.3                           | 0.243   |            |               |
| Tumor response                   |                                        |         |            |               |
| pCR vs non-pCR                   | 100 vs 74.2                            | 0.045   | 0.76 (0.10–1.73; 0.121) |
| ypT0–2 vs ypT3–4                 | 88.8 vs 66.9                           | 0.031   | 0.52 (0.25–2.61; 0.092) |
| ypN0 vs ypN1–2                   | 81.5 vs 71.6                           | 0.156   |            |               |
| Favorable vs unfavorable†         | 92.1 vs 62.4                           | 0.002   | 0.18 (0.02–0.79; 0.012) |
| Surgical distal margin           |                                        |         |            |               |
| Negative vs positive             | 83.4 vs 49.6                           | 0.009   | 0.26 (0.07–0.88; 0.026) |
| CRM                              |                                        |         |            |               |
| Negative vs positive             | 86.2 vs 40.9                           | 0.001   | 0.16 (0.03–0.80; 0.021) |

†Favorable: tumor regression Grade 3–4; unfavorable: tumor regression Grade 0–2. IG-IMRT = image-guided intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy, HR = hazard ratio, CI = confidence interval, P = P-value, 5-FU = 5-fluorouracil, pCR = pathologic complete response, CRM = circumferential resection margin.
| Study          | $n$ | Stage | Median RT dose | Chemotherapy                                                                 | Acute toxicity                                                                 | Late toxicity | Anus-preserving surgery | Tumor control |
|---------------|-----|-------|----------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------|------------------------|---------------|
| Parekh et al. | IMRT: 20 | All Stage II or III, except 2 with Stage I; 6 with Stage IVa | IMRT: 50 Gy/25 Fr (SIB) | 5-FU (300 mg/m$^2$): 67%; Cap (825 mg/m$^2$ twice daily): 33% | IMRT: (Grade 2+): *GI 30%; Hema: 10%; skin 35%; GU 0% | IMRT: 0 | IMRT: none | IMRT: 70% | IMRT: 21.4 | NR |
|               | IMRT: 25 Fr (SIB) | | | | | | | | | |
| Yang et al.   | IMRT: 98 | All Stage II or III except 14 with Stage I; 13 with Stage IV | IMRT: 50 Gy/25 Fr (SIB) | 5-FU (225 mg/m$^2$): 93%; Cap (875 mg/m$^2$ twice daily): 7% | IMRT (Grade 2+): *Diarrhea 10.8%; proctitis: 23%. | NR | NR | NR | NR | NR |
|               | 3DCRT: 79 | | | | | | | | | |
| Jabbour et al. | IMRT: 30 | All Stage II or III except 7 with Stage IV | IMRT: 50.4 Gy/28 Fr | 5-FU (225 mg/m$^2$) or Cap (825 mg/m$^2$ twice daily): 83.7%; Cap/oxaliplatin: 11.6% | IMRT (Grade 3+): diarrhea 3%; GU 0% | IMRT: 0 | NR | IMRT: 20 | *LRR: 6.7% | *DMR: 6.7% |
|               | 3DCRT: 56 | | | | | | | | | |
| Samuelian et al. | IMRT: 31 | All Stage II or III, but 22 with recurrent disease 11 for postoperative RT | IMRT: 50 Gy/25 Fr (SIB) | 5-FU (250 mg/m$^2$): 43.5%; Cap (875 mg/m$^2$ twice daily): 54.3% | IMRT (Grade 3+): GI 3%; Hema: 3%; skin: 3.2%. (Grade 2+): *GI: 32%; Hema: 45%; GU 16%; skin 10% | IMRT: 6.5% | *IMRT: 5.3% | IMRT: 82% | IMRT: 19 | NR |
|               | 3DCRT: 61 | | | | | | | | | |
| Drogé et al.  | VMAT: 81 | Stage II or III | VMAT and 3DCRT: 50.4 Gy/28 Fr | 5-FU (1000 mg/m$^2$ on Day 1-5 and 29-33 of the RT) | VMAT (Grade 3+): *proctitis 2%; Hema | NR | VMAT (Grade 3+): proctitis 3%; GU 3%; skin 0% | VMAT: 31% | VMAT: 20 | NR |
| Present study | HT: 45 | Stage II or III | HT: 50 Gy/25 Fr (SIB) | SR (Grade 3+): *proctitis 12%; Hema 4%; GU 3%; skin 7% | NR | 3DCRT (Grade 3+): proctitis 8%; GU 10%; skin 2% | 3DCRT: 23% | 3DCRT: 13 | NR |
|---------------|--------|----------------|----------------------|--------------------------------------------------------|-----|------------------------------------------------|--------|------|-----|
| 3DCRT: 107    |        |                | 3DCRT: 13          | SR (Grade 3+): *GI 6.7%; GU 0%; Hema 0%; skin: 2.2% | HT: 2.2% | HT (Grade 3+): GI 4.4%; GU 0% | HT: 84.4% | HT: 17.8 | 3DCRT: 47.9% | 3DCRT (Grade 3+): | 6.7% | 3DCRT: 17.8 | 84.4% | 17.8 | 6.7% |
| 3DCRT: 99     | 50.4 Gy/28 Fr | 3DCRT: 8.1% | 3DCRT (Grade 3+): *GI 15.1%; GU 3%; Hema 2%; skin: 3% | 3DCRT (Grade 3+): | 10.1%; GU 3.1% | 76.4% | DMR: 26.7% | 19.2% | 3DCRT: 19.2% | DMR: 33.3% |

*Statistically significant difference between IMRT and 3DCRT.
*aPostoperative complications.
*bIn tumors located within 0–5 cm from anal verge.
*cMedian follow-up time was 23 months in the 3DCRT group compared with 11 months in the IMRT group.
*dMedian follow-up time was 53 months in the 3DCRT group and 43 months in the IG-IMRT group.
NR = not reported, IMRT = intensity-modulated radiotherapy, 3DCRT = 3D conformal radiotherapy, pCR = pathological complete response, RT = radiotherapy, GI = gastrointestinal, Hema = hematological, GU = genitourinary, Cap = capecitabine, Fr = fraction, SIB = simultaneous integral boost, VMAT = volumetric-modulated arc therapy, HT = helical tomotherapy, LRR = local recurrence rate, DMR = distant metastasis rate.
patients treated with IMRT, we applied RTOG guidelines and indications in the anorectal contouring atlas to each patient receiving IMRT.

In the current study, patients underwent radiotherapy in the supine position, which could reduce set-up uncertainty. Certain studies have suggested that the prone position for the treatment of rectal cancer patients had the advantage of small-bowel sparing [4, 8, 32]. However, Beriwal et al. demonstrated no difference existed in GI toxicity between prone and supine IMRT [33]. In the Mayo Clinic, rectal cancer patients undergoing IMRT in the supine position experienced less GI toxicity [5]. The optimal positioning for pelvic irradiation remains controversial. Accordingly, we treated rectal cancer patients in the supine position because of reproducibility and tolerability. However, the question needs further investigations.

The current study has some limitations. First, this study had a retrospective design. Second, two chemotherapy regimens (infusional 5-FU and oral capecitabine) were used in combination with RT in this study. Evidence has not demonstrated any significant difference in tumor downstaging, survival profile and toxicity between capecitabine and infusional 5-FU in LARC patients undergoing preoperative CCRT [34, 35]. Therefore, the two different chemotherapy regimens had a limited effect on oncologic outcome.

CONCLUSIONS

In summary, IG-IMRT with a simultaneous integrated boost resulted in a lower GI toxicity and more favorable local control than did 3DCRT in patients with LARC, but no difference in distant metastasis rate or OS was observed between the two treatment modalities. Therefore, prospective, randomized studies are necessary to validate our observational study.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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