MR prediction of pathologic complete response and early-stage rectal cancer after neoadjuvant chemoradiation in patients with clinical T1/T2 rectal cancer for organ saving strategy

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Abstract
To evaluate the ability of magnetic resonance imaging (MRI) to predict pathologic complete response (pCR) after neoadjuvant chemoradiation therapy (CRT) in patients with clinical T1/T2 rectal cancer to indicate candidates for organ-saving strategies.

Between 2012 and 2016, 38 patients with clinical T1/T2 rectal cancer received neoadjuvant CRT. Radiologic complete response (rCR) was assigned when dense fibrotic tissue without tumor signal intensity was observed on post-CRT MRI. Surgical pathologic assessment was used to evaluate tumor regression. The association between rCR and the mural extent of the primary tumor, pCR, and pathologic T stage were analyzed.

In rCR patients, the pCR rate was higher; the odds of achieving pCR were 8.00 times higher than for non-rCR patients (P = .02). rCR patients were also more likely to have early-stage cancer than non-rCR patients (P = .01). Patients with partial extent of the primary tumor on post-CRT MRI were more likely to be diagnosed with early-stage cancer than those with transmural extent (P = .01).

rCR indicated by post-CRT MRI can be used as a supportive factor to predict pCR after neoadjuvant CRT in patients with clinical T1/T2 rectal cancer and can guide management decisions around organ-saving treatments.

Abbreviations: 5-FU = 5-fluorouracil, CR = complete response, CRT = chemoradiation therapy, TME = total mesorectal excision, MRI = magnetic resonance imaging, mTRG = MRI tumor regression grade, OR = odds ratio, pCR = pathologic complete response, PPV = positive predictive value, rCR = radiologic complete response.

Keywords: concurrent chemoradiotherapy, MRI, organ preservation, rectal cancer

1. Introduction
Total mesorectal excision (TME) is the standard treatment for most patients with rectal cancer, who underwent neoadjuvant chemoradiation therapy (CRT). After CRT, rectal cancers demonstrate variable degrees of tumor response, including pathologic complete response (pCR) in 15% to 27% of patients.[1] Patients with complete response (CR) or tumor downstaging after neoadjuvant CRT can achieve excellent local tumor control and a better quality of life, and organ-preserving treatments, such as watch-and-wait approach or local excision can be performed instead of TME.[2,3]

However, local tumor recurrence and compromised patient survival are major concerns in conducting organ-preserving treatments instead of radical surgery. A high rate of local tumor recurrence was observed in patients with T1/T2 rectal cancer after local excision alone.[4,5] CRT before local excision can decrease the incidence of local tumor recurrence,[5] and proper preoperative selection of patients with T1 rectal cancer after CRT lowers local recurrence.[6] Accordingly, organ preservation strategies can be adopted in a selected group of patients with optimal responses to CRT.[7–14]

Unfortunately, the accurate identification and prediction of pCR or early-stage cancer remains a major challenge.[15] Surgeons are often reluctant to deviate from TME because of concerns about viable cancer cells remaining in the rectal wall or mesorectal lymph nodes, even with clinical CR after CRT.[16] Therefore, organ-saving treatments should be carefully applied in only select situations in which clinical CR is conservatively defined to maximize its positive predictive value (PPV) for pCR.

Magnetic resonance imaging (MRI) is the recommended imaging tool for preoperative staging and post-treatment evaluation in patients with rectal cancer.[17,18] After CRT, a
soft tissue tumor is usually replaced by fibrotic tissue, and low signal intensity on a T2-weighted image is accepted as an indicator of CRT-induced fibrosis. Comparing low signal intensity fibrotic tissue to intermediate signal intensity residual tumors, the MRI and Rectal Cancer European Equivalence (MERCURY) study group proposed MRI tumor regression grades (mrTRG) for assessing patients with rectal cancer after CRT that were later demonstrated to be highly sensitive to detect pCR. In this study, we aimed to evaluate the ability of radiologic CR (rCR) via MRI, defined as either complete normalization of rectal wall or fibrotic scar only, to predict pCR or early-stage cancer after neoadjuvant CRT in patients with clinical T1/T2 rectal cancer to elucidate the identification of patient candidates for organ-saving strategies.

2. Materials and methods

2.1. Study population

Institutional review board at our institution approved this study, and the requirement for informed consent was waived. Between January 2012 and May 2016, we retrospectively registered 696 patients with clinical T1/T2 rectal cancer. Among these patients, 41 met the following inclusion criteria: they received neoadjuvant CRT before the surgery and performed initial and post-treatment MRI. Neoadjuvant CRT is not standard treatment for clinical T1/T2 rectal cancers, but, in this study, patients received neoadjuvant CRT due to:

1. suspicion of regional or pelvic sidewall lymph node metastasis,
2. sphincter preservation.

Since mrTRG is unreliable in the presence of a large mucinous component and precise cancer staging is difficult when tumor perforation has occurred, two patients were excluded. Additionally, one patient was excluded because he received TME 1 year after CRT due to preoperative diagnosis of three-vessel coronary artery disease. A total of 38 patients were included (Fig. 1). Characteristics of study patients are summarized in Table 1.

2.2. Neoadjuvant CRT

Chemotherapy regimens consisted of either capecitabine or 5-fluorouracil (5-FU) plus leucovorin, which oncologists decided based on discussions with patient. Radiation therapy consisted of a 45-Gy dose delivered to the whole pelvis in 25 fractions, followed by a 5.4-Gy boost targeting the primary tumor and the adjacent mesorectum delivered in 3 fractions. Patients receiving 5-FU plus leucovorin were administered two cycles of intravenous bolus injection of 5-FU (425 mg/m²/day) and leucovorin (20 mg/m²/day) during the first and fifth weeks of radiation therapy. Capecitabine patients received 850 mg/m² orally twice daily throughout radiotherapy. One of these patients was treated with a reduced dose of capecitabine due to creatinine elevation during treatment. Patients underwent curative surgery 6 to 10 weeks after the completion of CRT.

2.3. MRI examination

Baseline and post-CRT rectal MRI was performed using a 3.0-T MR scanner (Magnetom Tim Tio, Siemens Medical Solutions, Germany; or Ingenia, Philips Medical Systems, the Netherlands) with a pelvic phased-array surface coil. Intramuscular injection of 20 mg scopolamine butylbromide (Buscopan; Boehringer Ingelheim Korea, Republic of Korea) was performed 5 min before image acquisition to reduce bowel peristalsis. The scan protocol of the T2-weighted fast spin-echo sequence is as follows: repetition time/echo time (ms) 4714 to 6000/110 to 113; matrix 320×320 mm; section thickness/gap (mm) 3/3. Images were acquired in axial, oblique axial, oblique coronal, and sagittal.

![Flow diagram of patient selection.](image-url)
Tumor grade pathologic tumor regression grades[25]: reported pathologic diagnosis and used the Mandard grades for local excision in 2 patients. At our hospital, a pathologist
Pathologic analysis was performed after TME in 36 patients and rectal wall or
planes. Post-CRT MRI was performed 3 to 6 weeks after the completion of CRT and 2 to 6 weeks before surgery.

2.4. Image analysis

Two abdominal radiologists with 6 and 17 years of experience with rectal MRI, blinded to pathologic results, independently reviewed baseline and post-CRT MRI and evaluated the mural extent of the primary tumor as either partial or transmural (Fig. 2). Based on T2-weighted images of the post-CRT MRI, two readers assessed mrTRG, as defined by previous studies[22,23]:

1. complete radiologic response (fibrotic scar only);
2. predominantly fibrosis with minimal tumor signal;
3. >50% fibrosis with significant residual tumor;
4. mainly tumor signal;
5. identical appearance to original tumor.

In cases of discrepancy, radiologists verbally discussed discrepancies to reach a consensus. The 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting recommended reporting local tumor response after neoadjuvant CRT in three categories[24]:

1. completely normalized rectal wall;
2. fibrotic wall thickening without clear residual mass;
3. residual mass.

Considering the discrepancy between the mrTRG and ESGAR categories, we defined rCR as either complete normalization of rectal wall or fibrotic scar only. Corresponding with ESGAR 3, mrTRG 2 to 4 were categorized as radiologic non-CR (non-rCR).

2.5. Pathologic analysis

Pathologic analysis was performed after TME in 36 patients and local excision in 2 patients. At our hospital, a pathologist specialized in gastrointestinal pathology for more than 25 years reported pathologic diagnosis and used the Mandard grades for pathologic tumor regression grades[23]:

1. complete regression;
2. fibrosis with scattered tumor cells;
3. fibrosis and tumor cells with a preponderance of fibrosis;
4. fibrosis and tumor cells with a preponderance of cells;
5. tumor without changes of regression.

Based on the surgical pathologic report, Mandard grade 1 was categorized as pCR and grades 2 to 4 were categorized as non-pCR in this study; no patients in this study were Mandard grade 5. Final pathologic tumor stages were evaluated based on TNM system; ypT0, ypTis, and ypT1 cancers were considered early-stage cancer in this study.

2.6. Statistical analysis

Binary logistic regression was used to evaluate whether rCR and mural extent of the primary tumor predicted pCR and early-stage cancer. Additionally, the PPV of rCR and partial extent of primary tumor for pCR and early-stage cancer were calculated and analyzed using logistic regression in a generalized estimating equations model. Inter-reader agreement on mrTRG, rCR, and mural extent of primary tumor was analyzed by calculation of weighted kappa. Statistical analyses were performed using IBM SPSS version 24.0 (IBM Corp, Armonk, NY) and MedCalc (version 13.3, MedCalc Software, Mariakerke, Belgium). A P-value <.05 was considered statistically significant.

3. Results

3.1. Radiologic and pathologic assessment

The distributions of Mandard grade, T stage, and mrTRG among patients are summarized in Table 2. Out of 38 patients, 68.4% (26/38) were evaluated as rCR and, among non-rCR patients, mrTRG 2, 3, and 4 comprised 10.5% (4/38), 13.2% (5/38), and 7.9% (3/38) of patients, respectively. On baseline MRI, the primary tumor of 21 patients (21/38, 55.3%) involved partial thickness of the rectal wall and transmural extent of the tumor was observed in the remaining 17 patients (17/38, 44.7%). After CRT, the mural extent of the primary tumor decreased from transmural to partial in seven patients; in all, tumors were limited to partial extent in 73.7% (28/38) of patients on post-CRT MRI. Weighted kappas between the two readers were 0.557 for mrTRG, 0.588 for rCR, 0.694 for mural extent of primary tumor on baseline MRI, and 0.681 for mural extent of primary tumor on post-CRT MRI, collectively demonstrating a moderate degree of inter-reader agreement. According to final pathology reports, 18 patients (18/38, 47.4%) achieved pCR; among non-pCR patients, the tumors of 13 (13/38, 34.2%), 6 (6/38, 15.8%), and 1 (1/38, 2.6%) patients were Mandard grade 2, 3, and 4, respectively. Twenty-eight patients (28/38, 73.7%) had early-stage cancer, and 10 patients (10/38, 26.3%) had ypT2 rectal cancer. None of the patients were ypT3 or ypT4. Representative cases of rCR and non-rCR that were confirmed as pCR and non-pCR, respectively, are depicted in Figure 3.

3.2. Prevalence of pCR and early-stage cancer

Among the 26 patients evaluated as rCR, 16 patients (16/26, 61.5%) achieved pCR and 23 patients (23/26, 88.5%) were diagnosed with early-stage cancer (Table 3). In patients showing rCR, the odds ratio (OR) of achieving pCR was 8.00 (P = .02) and regression to early-stage cancer was 10.7 (P = .01), both of which

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Table 1

| Parameter                  | Value |
|----------------------------|-------|
| Sex                        |       |
| Women                      | 21    |
| Men                        | 17    |
| Age (years)                | Mean, 60 (range, 34–81) |
| CRT regimen                |       |
| 5-Fluorouracil with leucovorin | 15 |
| Capecitabine               | 23    |
| Post-CRT surgical method   |       |
| Total mesorectal excision  | 36    |
| Local excision             | 2     |
| Tumor location             |       |
| Upper rectum (AV > 12 cm)  | 1     |
| Mid-rectum (6 cm < AV ≤ 12 cm) | 4 |
| Lower rectum (AV ≤ 6 cm)   | 33    |
| Tumor grade                |       |
| Well-differentiated        | 11    |
| Moderately differentiated   | 25    |
| Poorly differentiated      | 2     |

AV = anal verge, CRT = chemoradiation therapy.
were statistically significant results. Among patients with partial extent of the primary cancer on baseline MRI, 11 patients (11/21, 52.4%) had pCR and 18 patients (18/21, 85.7%) received a pathologic diagnosis of early-stage cancer (Table 3). Partial extent of the tumor on baseline MRI did not predict both pCR (OR = 1.6, \( P = .49 \)) and early-stage cancer (OR = 4.2, \( P = .07 \)). Out of 28 patients with partial extent of the primary cancer on the post-CRT MRI, pCR, and early-stage cancer were found in 16 patients (16/28, 57.1%) and 24 patients (24/28, 85.7%), respectively (Table 3). Partial extent of the tumor on the post-CRT resulted in greater likelihood of pathologic diagnosis of early-stage cancer (OR = 9.0, \( P = .01 \)), whereas its impact on the odds of achieving pCR was statistically insignificant (OR = 5.3, \( P = .06 \)).

### 3.3. PPV of rCR and partial mural extent for pCR and early-stage cancer

Among 38 patients with clinical T1/T2 rectal cancer included in this study, 47.4% (18/38) achieved pCR, and early-stage cancer was achieved in 73.7% (28/38). PPVs of rCR, partial extent of tumor on baseline MRI, partial extent of tumor on post-CRT MRI, the combination of rCR with partial extent of tumor on baseline MRI, and the combination of rCR with partial extent of tumor on post-CRT MRI are summarized in Table 4. Although PPVs for pCR under all five conditions were numerically higher than the observed pCR rate, only rCR and rCR plus partial extent of tumor on post-CRT MRI showed statistically significantly higher PPV (61.5%, \( P = .01 \); 60.0%, \( P = .03 \), respectively). Compared to observed early stage cancer rate of 73.7%, PPVs for early-stage
In 59% of their cT2 patients, pCR was obtained, which is markedly higher than in routine CRT settings for advanced rectal cancer (15–27%). Therefore, we evaluated whether baseline and post-CRT MRI carry PPVs for selecting candidates to meet the conservative conditions necessary to perform organ-preserving strategies and avoid local recurrence.

In this study, patients with T1/T2 rectal cancer on baseline MRI were selected, and 47.4% achieved pCR after CRT and surgical excision, which exceeds the 15% to 27% rate of pCR reported for advanced rectal cancer. The PPV of rCR for pCR (61.5%, P = .01) was higher than the study-wide pCR rate (47.4%). PPV of rCR for early-stage cancer rate (88.5%, P = .02) was also higher than observed early stage cancer rate (73.7%). The PPVs of partial extent of the tumor on both baseline and post-CRT MRI for pCR and early-stage cancer were not statistically significantly higher than rCR. Moreover, combining rCR with mural extent on baseline or post-CRT MRI did not increase PPV relative to rCR alone.

Our study demonstrated that rCR can be used as a supportive imaging feature to predict pCR in patients with T1/T2 rectal cancer. These findings could help clinicians determine whether radical surgery or less aggressive treatment is more appropriate. Our study’s results differ from those of a previous study that indicates a low agreement between mrTRG and pathologic tumor regression, concluding that mrTRG could not replace pathologic tumor regression. The possible explanation for this disagreement is that more advanced cancer patients were included in that study than ours, which included only patients with cT1/T2 stage rectal cancer. Indeed, another study shows that favorable or unfavorable responses to CRT can be predicted by mrTRG evaluated on post-CRT MRI.

Some limitations exist in our study. Relatively small number of patients was included in this study, because standard treatment for clinical T1/T2 rectal cancer was not neoadjuvant CRT but surgery. Although we did not assess lymph node metastasis in post-CRT MRI, future studies should include lymph node evaluation because patients with lymph node metastasis are not candidates for local excision or watch-and-wait management. Finally, diffusion-weighted imaging (DWI) was not included in this study, although it has recently been used to evaluate the possibility of pCR after CRT.

In conclusion, rCR on post-CRT MRI can guide management decisions around organ-saving treatments after CRT in patients with clinical T1/T2 rectal cancer.

### Table 2

| Parameter                                              | Value     |
|--------------------------------------------------------|-----------|
| rCR (mrTRG 1)                                          | 68.4% (26/38) |
| Non-rCR (mrTRG 2–4)                                   |           |
| mrTRG 2                                                | 10.5% (4/38) |
| mrTRG 3                                                | 13.2% (5/38) |
| mrTRG 4                                                | 7.9% (3/38)  |
| Mural extent of the tumor on baseline MRI              |           |
| Partial extent                                         | 55.3% (21/38) |
| Transmural extent                                      | 44.7% (17/38) |
| Mural extent of the tumor on post-CRT MRI              |           |
| Partial extent                                         | 73.7% (28/38) |
| Transmural extent                                      | 26.3% (10/38) |
| Mandard grade                                          |           |
| Grade 1                                                | 47.4% (18/38) |
| Grade 2                                                | 34.2% (13/38) |
| Grade 3                                                | 15.8% (6/38)  |
| Grade 4                                                | 2.6% (1/38)  |
| Pathologic tumor stage                                 |           |
| Early-stage cancer (ypT0, ypTis, ypT1)                 |           |
| ypT0                                                  | 73.7% (28/38) |
| ypTis                                                 | 47.4% (19/38) |
| ypT1                                                  | 26.3% (10/38) |
| ypT2                                                  | 26.3% (10/38) |

### Table 3

| pCR rate | Odds ratio of achieving pCR (95% CI, P-value) | Early-stage cancer rate | Odds ratio to be early-stage cancer (95% CI, P-value) |
|----------|-----------------------------------------------|-------------------------|------------------------------------------------------|
| rCR/non-rCR |                                 |                         |                                                      |
| rCR, 61.5% (16/26) | 8.00 (95% CI = 1.45–44.30, P = .02) | rCR, 88.5% (23/26) | 10.7 (95% CI = 2.04–56.60, P = .01). |
| non-rCR, 16.7% (2/12) | 1.6 (95% CI = 0.43–5.71, P = .49) | non-rCR, 41.7% (5/12) |                                                      |
| Partial/transmural extent of the tumor on baseline MRI |                         |                         |                                                      |
| Partial extent, 52.4% (11/21) | 5.3 (95% CI = 0.95–29.81, P = .06) | Partial extent, 85.7% (18/21) | 4.2 (95% CI = 0.88–19.94, P = .07). |
| Transmural extent, 41.2% (7/17) |                         | Transmural extent, 58.8% (10/17) |                                                      |
| Partial/transmural extent of the tumor on post-CRT MRI |                         |                         |                                                      |
| Partial extent, 57.1% (16/28) |                         | Partial extent, 85.7% (24/28) | 9.0 (95% CI = 1.73–46.84, P = .01). |
| Transmural extent, 20.0% (2/10) |                         | Transmural extent, 40.0% (4/10) |                                                      |

CI = confidence interval, CRT = chemoradiation therapy, mrTRG = magnetic resonance imaging tumor regression grade, rCR = radiologic complete response.

1 Early-stage cancer includes pathologic T0, Tis, and T1.
2 MRI tumor regression grade (mrTRG) 1 was categorized as rCR, and mrTRG 2, 3, and 4 were categorized as non-rCR.
Table 4
Comparison of PPVs for pCR and early-stage cancer of six different conditions.

| Condition                                      | PPV for pCR | P   | PPV for early-stage cancer | P      |
|------------------------------------------------|-------------|-----|----------------------------|--------|
| Observed rate (cT1/T2)                         |             |     |                            |        |
| rCR                                            | 47.4% (18/38) |     | 73.7% (28/38)              |        |
| Partial extent on baseline MRI                 | 61.5% (16/26) | .01 | 88.5% (23/26)              | .02    |
| Partial extent on post-CRT MRI                 | 57.1% (16/28) | .05 | 85.7% (23/28)              | .07    |
| rCR and partial extent on baseline MRI         | 52.6% (10/19) | .52 | 84.2% (16/19)              | .14    |
| rCR and partial extent on post-CRT MRI         | 60.0% (13/22) | .23 | 88.9% (22/25)              | .02    |

CR = complete response, CRT = chemoradiation therapy, MRI = magnetic resonance imaging, pCR = pathologic complete response, PPV = positive predictive value, rCR = radiologic CR.

Early-stage cancer includes pathologic T0, Tis, and T1.

MRI tumor regression grade (mrTRG) 1 was categorized as rCR, and mrTRG 2, 3, and 4 were categorized as non-rCR.

Figure 3. Representative cases of radiologic complete response (rCR) and radiologic noncomplete response (non-rCR) in T2-weighted magnetic resonance imaging (MRI). Figures on the left and right are before and after neoadjuvant chemoradiation therapy (CRT), respectively. (A) A 70-year-old man with biopsy-confirmed rectal cancer in the right lateral wall of the mid-rectum. A change to homogenous, low signal intensity was seen post-CRT, which was categorized as rCR. The pathologic report indicated that pathologic complete response (pCR) (Mandard grade 1) was achieved. (B) A 65-year-old woman with biopsy-confirmed rectal cancer in the lower rectum. Although she was assessed as rCR on the post-CRT MRI, surgical pathology reported pathologic noncomplete response (non-pCR) (Mandard grade 2 and ypT1). (C) A 36-year-old man with biopsy-confirmed rectal cancer in the posterior wall of the lower rectum, evaluated as non-rCR; the final pathology report also indicated non-pCR (Mandard grade 3 and ypT3). (D) A 55-year-old woman with biopsy-confirmed rectal cancer in the upper rectum was evaluated as non-rCR post-CRT, but the final pathology reported pCR (Mandard grade 1).
Author contributions

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