

## Original Article

# Association of post-radiotherapy MRI response pattern with long-term survival outcome in rectal cancer patients undergoing neoadjuvant radiotherapy

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**Abstract:** Background: Pathologic complete response (pCR) after neoadjuvant radiotherapy has been used as a prognostic criterion in locally advanced rectal cancer. However, while MRI abnormalities may persist after treatment, this may be attributable to treatment-related changes rather than residual malignancy. In this study, we examined the correlation between post-radiotherapy MRI response pattern and pathologic response, and their association with long-term oncologic outcome. Methods: This retrospective observational cohort study included 225 patients with stage II-III rectal adenocarcinoma who received neoadjuvant radiotherapy prior to total mesorectal excision (TME) with curative intent between January 1, 2017 and December 31, 2023. Patients were classified according to pathologic response as pathologic complete response (pCR; ypT0N0, n = 48) or non-pathologic complete response (non-pCR, n = 177). Evaluated findings included baseline clinical characteristics, pretreatment MRI features, MRI response pattern after radiotherapy, pathologic results, recurrence, progression-free survival (PFS), and overall survival (OS). Data were analyzed with Kaplan-Meier method and Cox proportional hazards regression. Results: Overall, 21.3% of patients achieved pCR. These patients had significantly smaller baseline maximum tumor diameter (45.0 mm vs. 50.0 mm,  $P < 0.001$ ), smaller gross tumor volume (46.5 cm<sup>3</sup> vs. 60.8 cm<sup>3</sup>,  $P < 0.001$ ), and a lower prevalence of MRI-defined node-positive disease (41.7% vs. 64.4%,  $P = 0.008$ ) compared with the non-pCR group. Patients who achieved pCR had lower rates of recurrence or distant metastasis than those who did not (10.4% vs. 23.7%,  $P = 0.047$ ). Death occurred in 4.2% and 10.7% of patients, respectively ( $P = 0.262$ ). Median PFS was 51.0 months in the pCR group and 41.0 months in the non-pCR group; median OS was 62.5 months and 50.0 months, respectively. In univariable Cox regression analysis, pCR was associated with a lower risk of progression or recurrence (HR = 0.40, 95% CI 0.16-1.00;  $P = 0.050$ ); however, this association was attenuated after multivariable adjustment (adjusted HR = 0.46, 95% CI 0.20-1.08;  $P = 0.073$ ). Residual DWI hyperintensity (83.3%), tumor-bed fibrosis (97.9%), fibrotic scar formation (68.8%), and submucosal edema (68.8%) were frequently observed in pCR patients. In the pCR group, none of these post-treatment MRI response patterns was significantly associated with progression-free or overall survival. Conclusion: Patients with locally advanced rectal cancer who achieved pathologic complete response after neoadjuvant therapy had a lower recurrence rate, while the observed difference in overall survival did not reach statistical significance. Despite complete pathologic remission, abnormal MRI findings often persisted after treatment and were not significantly associated with unfavorable prognosis within the pCR cohort. This study suggests that post-treatment MRI abnormalities should be interpreted in conjunction with pathologic and clinical findings, rather than being automatically attributed to residual disease.

**Keywords:** Rectal cancer, neoadjuvant radiotherapy, pathological complete response, magnetic resonance imaging, progression-free survival, overall survival, diffusion-weighted imaging, tumor-bed fibrosis, prognosis, tumor regression

## Introduction

Rectal cancer is a common malignancy worldwide and a leading cause of cancer-related morbidity and mortality. Globally, colorectal

cancer ranks among the leading malignancies in both incidence and mortality, and rectal cancer accounts for approximately one-third of all colorectal cancers (CRC). Despite recent advances in screening programs, surgical te-

chnique, radiotherapy, and systemic therapy, locally advanced rectal cancer (LARC) continues to be a significant therapeutic challenge due to its tendency to recur, invade local tissues, metastasize to lymph nodes, and impair function following treatment. Multimodal treatment regimens incorporating neoadjuvant radiotherapy (or chemoradiotherapy) followed by total mesorectal excision (TME) have significantly improved local control and long-term oncologic outcomes over the past two decades [1]. However, treatment response varies considerably among patients, underscoring the need for reliable prognostic biomarkers to guide individualized therapy.

Preoperative radiotherapy contributes to disease control by inducing tumor regression, sterilizing microscopic disease, and increasing the likelihood of complete resection. Neoadjuvant therapy has been shown to be effective at reducing local recurrence rates and improving sphincter preservation in suitably selected patients in clinical trials. However, the response to radiotherapy is variable, ranging from partial regression to complete eradication of viable tumor cells [2]. This variation has led to a renewed interest in the development of imaging and pathologic markers that can accurately reflect treatment effectiveness and, ultimately, survival outcome [3-5]. Pathologic complete response (pCR; ypT0N0), defined as the absence of viable tumor cells in the surgical specimen after neoadjuvant therapy, is one of the strongest prognostic markers in rectal cancer [3, 4]. Patients who achieve pCR typically have a lower risk of recurrence and distant metastasis, as well as longer disease-free and overall survival, compared to those with residual disease. Accurate identification of patients who have achieved complete tumor eradication has become increasingly clinically relevant, particularly with the growing adoption of organ-preservation strategies and “watch-and-wait” management. Thus, prior to surgery, it is now crucial to assess treatment response accurately.

Current guidelines recommend MRI as the best imaging modality for initial staging and post-treatment evaluation of rectal cancer. Several MRI techniques are well suited for this purpose. T2-weighted imaging provides excellent soft-tissue resolution and detailed anatomic

assessment of the rectal wall, mesorectal fascia, and surrounding structures [6-8]. Moreover, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping provide functional data reflecting treatment-induced changes in tumor cellularity. Dynamic contrast-enhanced (DCE) imaging may also help differentiate viable residual tumor from treatment-related fibrosis. Because of these advantages, MRI has become an essential imaging technique for determining response to preoperative radiotherapy [9-13].

Although MRI has been used frequently, the interpretation of post-radiotherapy MRI remains challenging. Radiotherapy induces a complex cascade of tissue changes, including fibrosis, edema, inflammatory reaction, mucin deposition, vascular remodeling, and scar formation. These post-treatment changes may persist for months and may mimic residual tumor on imaging. Even patients who subsequently show pathologic complete response have common findings of residual wall thickening, diffusion restriction, and enhancement abnormalities [13-16]. Conversely, even when imaging suggests a favorable response, microscopic tumor cells may remain. In clinical practice, this means that there is frequently a discrepancy between radiologic and pathologic diagnosis [17-19]. Several MRI classification systems have been proposed, such as the magnetic resonance tumor regression grade (mrTRG), to help assess response. The mrTRG system may more representatively reflect the extent of fibrosis and the amount of remaining tumor cells in the treated lesion and provide a more uniform assessment of treatment response [20-22]. Moderate correlations have been reported between mrTRG and pathologic outcome in the past, which may imply a potential prognostic role of mrTRG. However, substantial inter-observer variability and limited predictive value have hindered its widespread clinical adoption. In addition, some post-treatment MRI response features are not well-characterized with respect to biological significance and prognostic consequences. A further challenge is the growing recognition that conventional MRI cannot reliably distinguish complete responders from those with residual disease [23-25]. Treatment-related fibrosis may exhibit imaging features similar to those of recurrent tumor [26-28]. Likewise, residual hyperintensi-

ty on DWI can be seen in cases of complete pathologic response, which may lead to overestimation of residual disease. The potential clinical implications of this diagnostic uncertainty may extend to decisions about clinical management, surgical planning, surveillance frequency, and eligibility for organ-preservation technique. Therefore, a deeper understanding of the MRI response after radiotherapy and its effect on survival is essential.

Numerous studies have investigated the ability of MRI to predict pCR, but fewer studies have focused on MRI response findings as prognostic factors after neoadjuvant radiotherapy in this population [29-31]. Most reported studies have focused on diagnostic accuracy findings such as sensitivity and specificity, whereas the association between post-treatment imaging findings and long-term clinical outcomes remains less well characterized. Furthermore, most previous studies have had short follow-up duration, inconsistent definitions of MRI response features, or small sample sizes with heterogeneous treatment protocols. It remains unclear whether persistent post-treatment MRI abnormalities independently predict poor prognosis, or whether other MRI patterns provide additional prognostic information beyond pathologic assessment.

These are areas in which further research is needed to better characterize the MRI response pattern and its association with pathologic response and long-term survival in patients with rectal cancer treated with neoadjuvant radiotherapy [32]. An improved understanding of these relationships might result in more effective post-treatment risk stratification, more effective surveillance stratification, and optimized individual therapeutic choice.

Although MRI abnormalities after radiotherapy are common, it remains unclear whether individual MRI abnormalities independently influence long-term prognosis.

### Materials and methods

#### *Study design and setting*

This retrospective, single-center observational cohort study evaluated the association between post-radiotherapy magnetic resonance imaging (MRI) response pattern and long-term

oncologic outcome in patients with locally advanced rectal adenocarcinoma treated with neoadjuvant radiotherapy followed by curative-intent surgery. Consecutive eligible patients who initiated neoadjuvant radiotherapy between January 2017 and December 2023 at a tertiary referral cancer center were included to minimize selection bias.

Clinical, radiologic, pathologic, treatment-related, and follow-up data were retrospectively extracted from institutional electronic medical records, radiotherapy databases, radiology archives, pathology reports, and follow-up registries using standardized data collection forms.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine (Approval No. 2026-1013). Owing to the retrospective nature of the study, patient data were anonymized before analysis to ensure confidentiality.

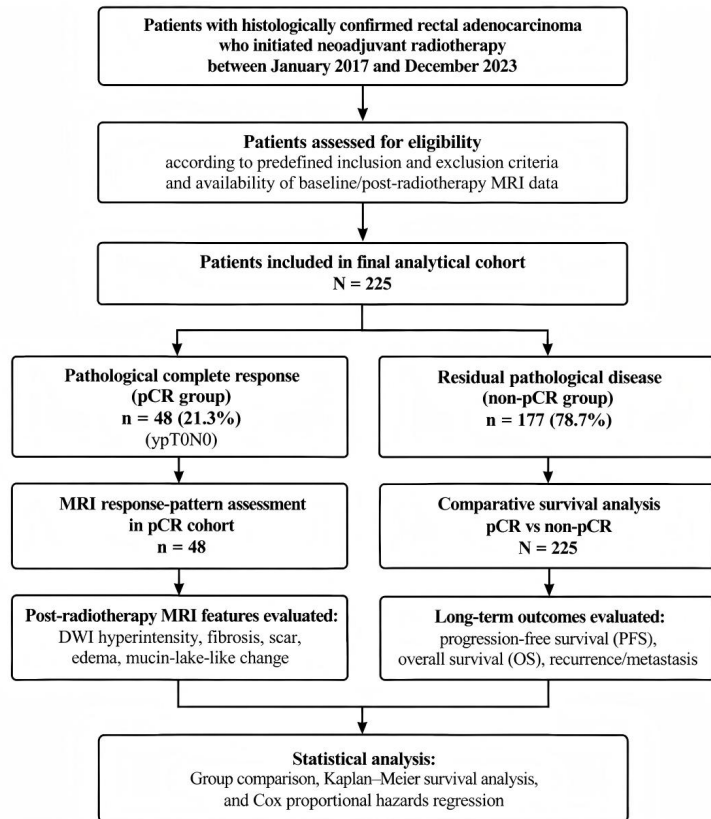
#### *Study population*

A total of 225 patients with histologically confirmed rectal adenocarcinoma who underwent neoadjuvant radiotherapy followed by radical surgery were included in the final analysis (**Figure 1**). Patients were classified according to pathologic response after surgery into the pathologic complete response (pCR) group (ypT0N0, n = 48) and the non-pathologic complete response (non-pCR) group (n = 177).

Pathologic complete response was defined as the complete absence of viable tumor cells in both the primary tumor site and regional lymph nodes (ypT0N0). Patients with any residual microscopic or macroscopic tumor identified on pathologic examination were classified as non-pCR.

#### *Inclusion criteria*

Patients were eligible if they fulfilled all of the following criteria: (1) Age  $\geq$  18 years. (2) Histologically confirmed rectal adenocarcinoma. (3) Clinical stage II-III disease before treatment. (4) Received neoadjuvant radiotherapy between January 2017 and December 2023. (5) Baseline pelvic MRI before treatment. (6) Post-radiotherapy pelvic MRI before surgery.



Abbreviations: MRI, magnetic resonance imaging; pCR, pathological complete response; DWI, diffusion-weighted imaging; PFS, progression-free survival; OS, overall survival.

**Figure 1.** Study flow diagram. Flow diagram illustrating patient selection and study inclusion. A total of 225 patients with histologically confirmed locally advanced rectal adenocarcinoma who underwent neoadjuvant radiotherapy followed by curative-intent total mesorectal excision between January 2017 and December 2023 were included in the final analysis. Patients were classified according to pathologic response into pathologic complete response (pCR; ypT0N0) and non-pathologic complete response (non-pCR) groups after application of the predefined inclusion and exclusion criteria.

- (7) Curative-intent total mesorectal excision (TME).
- (8) Complete pathological evaluation.
- (9) Available clinical follow-up data.

#### Exclusion criteria

Patients were excluded if they met any of the following criteria: (1) Distant metastatic disease at diagnosis. (2) Previous pelvic radiotherapy. (3) History of another malignancy within the preceding five years. (4) Incomplete or poor-quality MRI examinations unsuitable for interpretation. (5) Missing pathologic response assessment. (6) Incomplete treatment records or follow-up information. (7) Palliative treatment intent or non-curative surgery.

#### Neoadjuvant radiotherapy and treatment protocol

All patients were discussed at a multidisciplinary tumor board before treatment initiation. Neoadjuvant treatment was administered according to institutional protocols based on clinical stage, tumor location, patient characteristics, and multidisciplinary recommendations.

Patients received either long-course radiotherapy (45.0–50.4 Gy delivered in 25–28 fractions) or short-course radiotherapy according to contemporary treatment guidelines. Concurrent fluoropyrimidine-based chemotherapy was administered when clinically indicated. Radiotherapy was delivered using three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT).

Following completion of neoadjuvant therapy, patients underwent curative-intent total mesorectal excision. The interval between completion of radiotherapy and surgery was determined through multidisciplinary assessment and individual clinical considerations.

#### MRI acquisition and imaging assessment

Pelvic MRI examinations were performed before initiation of neoadjuvant therapy and repeated after completion of radiotherapy before surgery using standardized institutional imaging protocols.

The MRI protocol included: (1) High-resolution T2-weighted imaging in axial, sagittal, and coronal planes. (2) Diffusion-weighted imaging (DWI). (3) Apparent diffusion coefficient (ADC) mapping. (4) Contrast-enhanced T1-weighted imaging when clinically indicated.

All MRI examinations were independently reviewed by experienced gastrointestinal radi-

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ologists who were blinded to pathologic outcome.

Because of the retrospective design, standardized quantitative MRI biomarkers - including ADC threshold values, quantitative DWI signal intensity measurements, and post-treatment volumetric assessments - were not consistently available for all patients. Therefore, MRI assessment focused primarily on qualitative imaging response patterns.

### *Baseline MRI variables*

The following pretreatment MRI characteristics were recorded: (1) Maximum tumor longitudinal diameter (mm). (2) Maximum tumor thickness (mm). (3) Gross tumor volume (GTV, cm<sup>3</sup>). (4) Clinical T stage. (5) MRI-defined nodal status. (6) Mesorectal fascia involvement. (7) Extramural vascular invasion.

Tumor dimensions and volumes were measured using standardized institutional radiologic techniques.

### *Post-radiotherapy MRI response evaluation*

Post-treatment MRI examinations were evaluated to characterize qualitative treatment-related response patterns.

The following MRI features were recorded: (1) Residual diffusion-weighted imaging (DWI) hyperintensity: persistent high signal intensity within the treated tumor bed on DWI. (2) Tumor-bed fibrosis: replacement of the primary tumor by low T2-signal fibrotic tissue without visible residual tumor. (3) Fibrotic scar formation: mature scar tissue replacing the original tumor site. (4) Submucosal edema: residual mural thickening and high T2 signal consistent with treatment-related edema. (5) Mucin-lake-like changes: high T2 signal intensity representing acellular mucin accumulation. (6) Magnetic resonance tumor regression grade (mrTRG): evaluated according to MRI-based assessment of fibrosis and residual tumor signal abnormalities.

Terminology describing post-treatment MRI findings was standardized throughout the manuscript to improve consistency.

### *Pathologic assessment*

All surgical specimens were processed according to standardized pathologic protocols. Histopathologic examination was independent-

ly performed by specialized gastrointestinal pathologists who were blinded to MRI findings.

Pathologic evaluation included: (1) Tumor regression grade. (2) ypT stage. (3) ypN stage. (4) Circumferential resection margin status. (5) Lymphovascular invasion. (6) Perineural invasion. (7) Number of lymph nodes examined. (8) Number of metastatic lymph nodes.

Pathologic complete response was defined as ypT0N0 with no residual viable tumor identified in either the primary tumor or regional lymph nodes.

### *Follow-up and outcome measures*

Patients were followed according to institutional colorectal cancer surveillance protocols.

Routine follow-up included: (1) Clinical examination. (2) Serum carcinoembryonic antigen (CEA) assessment. (3) Colonoscopy. (4) Computed tomography. (5) Pelvic MRI when clinically indicated.

The median follow-up duration was 48 months and 46 months separately. Patients were followed until disease recurrence, death, loss to follow-up, or study completion.

### *Outcome definitions*

The primary endpoint was progression-free survival (PFS), defined as the interval from curative-intent surgery to the first occurrence of local recurrence, regional recurrence, distant metastasis, disease progression, or death from any cause.

The secondary endpoint was overall survival (OS), defined as the interval from surgery to death from any cause.

Recurrence events were categorized as: (1) Local recurrence. (2) Regional nodal recurrence. (3) Distant metastasis.

Where data permitted, recurrence subtypes were analyzed separately.

### *Data collection and management*

Clinical, radiologic, pathologic, treatment, and survival data were extracted using standardized data collection forms. Data verification was independently performed by two investigators, and discrepancies were resolved by consensus review to minimize extraction errors.

### Statistical analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test and are presented as mean  $\pm$  standard deviation or median (interquartile range), as appropriate. Between-group comparisons were performed using the independent-samples *t* test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

Survival time was calculated from the date of curative-intent surgery to the occurrence of an event or the last documented follow-up. Kaplan-Meier curves were generated for PFS and OS, and survival distributions were compared using the two-sided log-rank test.

Cox proportional hazards regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Univariable analyses were initially performed. Variables considered clinically relevant or demonstrating statistical significance in univariable analyses, including baseline tumor long diameter, gross tumor volume, MRI-defined nodal status, tumor differentiation, baseline CEA level, and radiotherapy regimen, were entered into multivariable Cox proportional hazards models to identify independent predictors of PFS and OS.

Subgroup analyses were performed according to radiotherapy regimen (long-course versus short-course) and, where feasible, according to individual post-radiotherapy MRI response features within the pCR cohort.

All statistical analyses were performed using SPSS version 26. A two-sided *P* value  $< 0.05$  was considered significant.

## Results

### Patient selection

The patient selection process is summarized in **Figure 1**. Consecutive patients with histologically confirmed rectal adenocarcinoma who received neoadjuvant radiotherapy between January 2017 and December 2023 were screened for eligibility. After application of the predefined inclusion and exclusion criteria, a total of 225 patients were included in the final analysis. Patients were subsequently stratified according to pathologic response into the pathologic complete response (pCR) group

(*n* = 48) and the non-pathologic complete response (non-pCR) group (*n* = 177).

### Baseline clinical, radiological, and treatment characteristics

Baseline demographic, clinical, radiological, and treatment characteristics of the study population are presented in **Table 1**. Overall, the two groups were generally comparable with respect to demographic characteristics, including age and sex distribution, as well as baseline clinicopathologic variables. However, significant differences were observed in MRI-derived measures of tumor burden. Patients who subsequently achieved pCR demonstrated significantly smaller pretreatment tumor size and gross tumor volume compared to those who had residual disease following neoadjuvant therapy.

Differences in MRI-defined nodal status, baseline tumor characteristics, and treatment-related variables are summarized in **Table 1**. Radiotherapy regimen was also evaluated as an important treatment-related variable potentially associated with clinical outcomes.

### Treatment response and pathological outcome

Pathologic treatment response following neoadjuvant radiotherapy is summarized in **Table 2**. All patients underwent curative-intent total mesorectal excision after completion of neoadjuvant treatment. Surgical margin status, pathological tumor regression, ypT stage, ypN stage, lymphovascular invasion, perineural invasion, and lymph node characteristics were compared between the pCR and non-pCR groups.

Patients achieving pCR demonstrated more favorable pathological findings, including complete tumor regression and absence of residual nodal disease.

### Long-term oncologic outcome

Long-term oncologic outcomes are summarized in **Table 3**. Patients who achieved pathologic complete response experienced lower rates of disease recurrence, distant metastasis, and death compared to patients with residual disease following neoadjuvant treatment. Recurrence outcomes, including local recurrence, regional recurrence, and distant metastasis, are comprehensively presented and compared between groups in **Table 3**.

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**Table 1.** Baseline demographic, clinical, radiologic, and treatment characteristics

| Variable                              | Overall (n = 225) | pCR (n = 48) | Non-pCR (n = 177) | P value |
|---------------------------------------|-------------------|--------------|-------------------|---------|
| Age (years), median (IQR)             | 61 (54-68)        | 59 (53-66)   | 62 (55-69)        | 0.214   |
| Male                                  | 146 (64.9%)       | 30 (62.5%)   | 116 (65.5%)       | 0.702   |
| Female                                | 79 (35.1%)        | 18 (37.5%)   | 61 (34.5%)        |         |
| Moderately differentiated             | 163 (72.4%)       | 37 (77.1%)   | 126 (71.2%)       | 0.441   |
| Poorly differentiated                 | 62 (27.6%)        | 11 (22.9%)   | 51 (28.8%)        |         |
| Baseline CEA (ng/mL)                  | 6.8 ± 3.5         | 5.6 ± 2.9    | 7.1 ± 3.8         | 0.032   |
| Maximum tumor diameter (mm)           | 49.0 (43-56)      | 45.0 (40-50) | 50.0 (45-57)      | < 0.001 |
| Tumor thickness (mm)                  | 18.4 ± 5.1        | 16.2 ± 4.3   | 19.0 ± 5.2        | 0.008   |
| Gross tumor volume (cm <sup>3</sup> ) | 57.8 (39-74)      | 46.5 (34-60) | 60.8 (44-77)      | < 0.001 |
| Clinical T3/T4                        | 188 (83.6%)       | 39 (81.3%)   | 149 (84.2%)       | 0.618   |
| Clinical N-positive                   | 134 (59.6%)       | 20 (41.7%)   | 114 (64.4%)       | 0.008   |
| Mesorectal fascia involvement         | 71 (31.6%)        | 10 (20.8%)   | 61 (34.5%)        | 0.081   |
| EMVI positive                         | 59 (26.2%)        | 8 (16.7%)    | 51 (28.8%)        | 0.096   |
| Long-course RT                        | 183 (81.3%)       | 41 (85.4%)   | 142 (80.2%)       | 0.412   |
| Short-course RT                       | 42 (18.7%)        | 7 (14.6%)    | 35 (19.8%)        |         |

**Table 2.** Pathologic outcomes

| Variable                    | pCR | Non-pCR    | P value |
|-----------------------------|-----|------------|---------|
| ypN positive                | 0   | 79 (44.6%) | < 0.001 |
| CRM positive                | 0   | 6 (3.4%)   | 0.204   |
| Lymphovascular invasion     | 0   | 39 (22.0%) | < 0.001 |
| Perineural invasion         | 0   | 31 (17.5%) | 0.002   |
| Median lymph nodes examined | 18  | 17         | 0.383   |

**Table 3.** Long-term oncologic outcomes

| Outcome                   | pCR        | Non-pCR    | P value |
|---------------------------|------------|------------|---------|
| Median follow-up (months) | 48 (12-89) | 46 (11-88) | 0.642   |
| Local recurrence          | 1 (2.1%)   | 10 (5.6%)  | 0.463   |
| Regional recurrence       | 0          | 5 (2.8%)   | 0.584   |
| Distant metastasis        | 4 (8.3%)   | 35 (19.8%) | 0.048   |
| Overall recurrence        | 5 (10.4%)  | 42 (23.7%) | 0.047   |
| Death                     | 2 (4.2%)   | 19 (10.7%) | 0.262   |

Kaplan-Meier survival curves demonstrated improved progression-free survival (PFS) and overall survival (OS) among patients achieving pCR compared to those with non-pCR (**Figure 2**).

### Cox proportional hazards regression analysis

The results of the univariable and multivariable Cox proportional hazards regression analyses are presented in **Tables 4-6**.

By univariable analyses, pathologic complete response was associated with improved progression-free survival and overall survival compared with non-pCR. Multivariable Cox regres-

sion models were subsequently constructed after adjustment for clinically relevant baseline variables, including maximum tumor diameter, gross tumor volume, MRI-defined nodal status, tumor differentiation, baseline carcinoembryonic antigen (CEA) level, and radiotherapy regimen. Adjusted hazard ratios with corresponding 95% confidence intervals are presented in **Table 6**.

### Radiotherapy regimen subgroup analysis

Comparisons were performed between patients receiving long-course and short-course radiotherapy. Baseline charac-

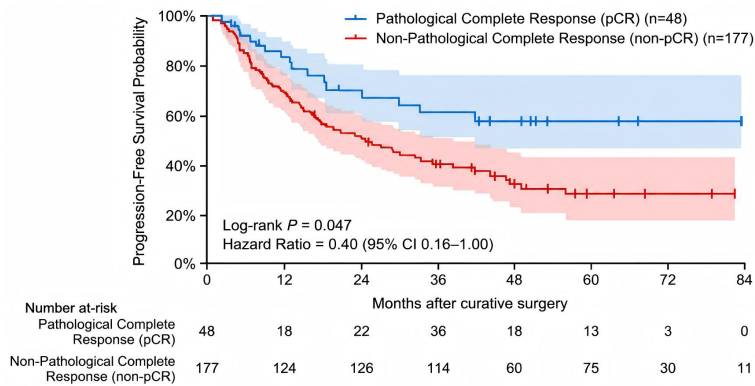
teristics, pathologic response, MRI response patterns, progression-free survival, and overall survival were evaluated according to treatment regimen.

Kaplan-Meier survival analyses comparing radiotherapy strategies are presented in **Figure 3A** (PFS) and **Figure 3B** (OS).

### Post-radiotherapy MRI response patterns in patient with pathologic complete response

Post-treatment qualitative MRI findings among patients with pathologic complete response are summarized in **Tables 7, 8**. Persistent treat-

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**Figure 2.** Kaplan-Meier curves demonstrating progression-free survival (PFS) according to pathologic response following neoadjuvant radiotherapy. Note: Patients achieving pathologic complete response (pCR) demonstrated improved progression-free survival compared to patients with residual pathologic disease (non-pCR). Survival distributions were compared using the two-sided log-rank test.

**Table 4.** Univariable Cox regression

| Variable            | HR   | 95% CI    | P value |
|---------------------|------|-----------|---------|
| pCR                 | 0.40 | 0.16-1.00 | 0.050   |
| Tumor long diameter | 1.03 | 1.01-1.05 | 0.008   |
| Gross tumor volume  | 1.02 | 1.01-1.03 | 0.005   |
| Clinical N-positive | 1.61 | 1.02-2.54 | 0.039   |
| Long-course RT      | 0.89 | 0.56-1.42 | 0.633   |

**Table 5.** Multivariate Cox regression for progression-free survival

| Variable            | Adjusted HR | 95% CI    | P value |
|---------------------|-------------|-----------|---------|
| pCR                 | 0.46        | 0.20-1.08 | 0.073   |
| Tumor long diameter | 1.02        | 1.00-1.04 | 0.041   |
| Gross tumor volume  | 1.01        | 1.00-1.03 | 0.029   |
| Clinical N-positive | 1.47        | 0.93-2.34 | 0.097   |
| Baseline CEA        | 1.04        | 1.01-1.08 | 0.023   |
| Long-course RT      | 0.92        | 0.59-1.44 | 0.714   |

**Table 6.** Multivariate Cox regression for overall survival

| Variable            | Adjusted HR | 95% CI    | P value |
|---------------------|-------------|-----------|---------|
| pCR                 | 0.39        | 0.09-1.63 | 0.197   |
| Tumor long diameter | 1.03        | 1.00-1.06 | 0.044   |
| Clinical N-positive | 1.71        | 0.88-3.29 | 0.111   |
| Baseline CEA        | 1.06        | 1.01-1.11 | 0.019   |

ment-related MRI abnormalities remained common despite complete pathologic eradication of tumor. Frequently observed imaging findings included tumor-bed fibrosis, residual diffusion-weighted imaging (DWI) hyperintensity, fibrotic scar formation, submucosal edema, and mucin-lake-like changes.

To determine the prognostic significance of these imaging findings, survival analyses were performed according to individual MRI response patterns within the pCR cohort. Progression-free survival according to individual MRI response patterns within the pCR cohort is summarized in **Table 9**. Kaplan-Meier curves for progression-free survival according to residual DWI hyperintensity, tumor-bed fibrosis, fibrotic scar formation, submucosal edema, and mucin-lake-like changes are presented in **Figure 4A, 4B**, while the corresponding Cox regression analyses are summarized in **Table 10**.

### Recurrence pattern analysis

Patterns of disease recurrence are summarized in **Table 3**. Recurrence events were categorized as local recurrence, regional nodal recurrence, distant metastasis, or multiple-site recurrence. Comparisons between the pCR and non-pCR groups demonstrated differences in the distribution of recurrence patterns, with patients achieving pathologic complete response experiencing fewer recurrence events overall.

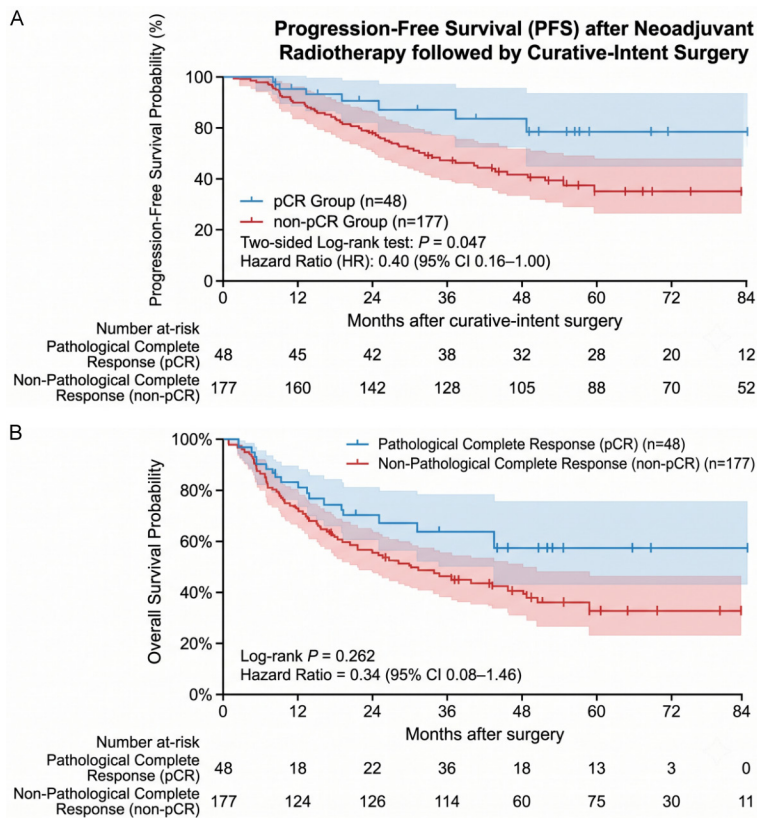
Representative post-radiotherapy MRI findings observed in patients with pathologic complete response are illustrated in **Figure 5**, demonstrating the spectrum of persistent treatment-related imaging abnormalities despite complete pathological tumor eradication.

malities despite complete pathological tumor eradication.

### Summary of major findings

Overall, patients who achieved pathologic complete response demonstrated a lower pre-

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**Figure 3.** A. Kaplan-Meier curve for progression-free survival. B. Kaplan-Meier curve for overall survival.

**Table 7.** MRI response patterns in pCR patients (n = 48)

| MRI Finding                 | Present n (%) |
|-----------------------------|---------------|
| Tumor-bed fibrosis          | 47 (97.9%)    |
| Residual DWI hyperintensity | 40 (83.3%)    |
| Fibrotic scar formation     | 33 (68.8%)    |
| Submucosal edema            | 33 (68.8%)    |
| Mucin-lake-like changes     | 10 (20.8%)    |

treatment MRI-defined tumor burden, more favorable pathologic characteristics following neoadjuvant therapy, reduced rates of disease recurrence, and improved long-term oncologic outcomes compared to patients with residual disease. Although qualitative MRI abnormalities frequently persisted after treatment among patients with pCR, their prognostic significance was further evaluated using subgroup survival analyses and multivariable regression models.

### Discussion

The present study evaluated the association between post-radiotherapy magnetic resonance imaging (MRI) response pattern and long-

term oncologic outcome in patients with locally advanced rectal adenocarcinoma treated with neoadjuvant radiotherapy followed by curative-intent surgery. Among the 225 patients included, 48 (21.3%) achieved a pathologic complete response (pCR). Patients achieving pCR demonstrated lower pre-treatment MRI-defined tumor burden, more favorable pathologic findings, lower recurrence rates, and improved long-term survival outcomes than patients with residual disease. Furthermore, qualitative MRI abnormalities frequently persisted after treatment despite complete pathological tumor eradication, highlighting the limitations of conventional MRI in distinguishing treatment-related changes from residual viable tumor.

The observed pCR rate of 21.3% is consistent with previously reported rates of approximately 15%-30% following neoadjuvant radiotherapy or chemoradiotherapy for locally advanced rectal cancer. Variability in reported pCR rates across studies is likely attributable to differences in patient selection, tumor stage distribution, neoadjuvant treatment protocols, radiotherapy

techniques, chemotherapy use, surgical timing, and pathologic assessment criteria. Nevertheless, our findings reinforce existing evidence that a substantial proportion of patients can achieve complete tumor eradication following neoadjuvant treatment. This has important implications for contemporary rectal cancer management, particularly as interest continues to grow in organ-preservation strategies and non-operative “watch-and-wait” approaches, where accurate identification of complete responders is critical [14-17].

Patients who achieved pCR experienced more favorable oncologic outcomes than those with residual disease. Although the study was not

**Table 8.** Post-radiotherapy MRI response patterns in patients with pathologic complete response (pCR) (n = 48)

| MRI Response Pattern                                     | Present, n (%) | Absent, n (%) |
|----------------------------------------------------------|----------------|---------------|
| Residual diffusion-weighted imaging (DWI) hyperintensity | 40 (83.3)      | 8 (16.7)      |
| Tumor-bed fibrosis                                       | 47 (97.9)      | 1 (2.1)       |
| Fibrotic scar formation                                  | 33 (68.8)      | 15 (31.2)     |
| Submucosal edema                                         | 33 (68.8)      | 15 (31.2)     |
| Mucin-lake-like changes                                  | 10 (20.8)      | 38 (79.2)     |
| mrTRG 1                                                  | 29 (60.4)      | -             |
| mrTRG 2                                                  | 12 (25.0)      | -             |
| mrTRG 3                                                  | 5 (10.4)       | -             |
| mrTRG 4                                                  | 2 (4.2)        | -             |
| mrTRG 5                                                  | 0 (0.0)        | -             |

Abbreviations: DWI, diffusion-weighted imaging; mrTRG, magnetic resonance tumor regression grade.

**Table 9.** Survival according to MRI features within the pCR cohort

| MRI Finding                 | HR for PFS | 95% CI    | P value |
|-----------------------------|------------|-----------|---------|
| Residual DWI hyperintensity | 1.18       | 0.39-3.59 | 0.771   |
| Tumor-bed fibrosis          | 0.94       | 0.11-8.08 | 0.956   |
| Fibrotic scar formation     | 0.88       | 0.29-2.66 | 0.824   |
| Submucosal edema            | 1.14       | 0.37-3.46 | 0.822   |
| Mucin-lake-like changes     | 1.42       | 0.44-4.56 | 0.553   |

powered to detect statistically significant differences across all survival endpoints, recurrence events were less frequent among patients with pCR, and survival analyses consistently demonstrated improved progression-free survival (PFS) and overall survival (OS). These findings are consistent with previous studies identifying pCR as one of the strongest prognostic indicators following neoadjuvant therapy [18-20].

The biological mechanisms underlying the favorable prognosis associated with pCR are likely multifactorial. Complete pathologic response may reflect increased radiosensitivity, lower intrinsic tumor aggressiveness, improved tumor oxygenation, favorable tumor microenvironment characteristics, and a more effective host immune response. Furthermore, complete eradication of the primary tumor may serve as a surrogate marker for effective systemic disease control, thereby reducing the likelihood of occult micrometastatic disease. Collectively, these mechanisms may explain the lower rates of local recurrence and distant metastasis observed among complete responders.

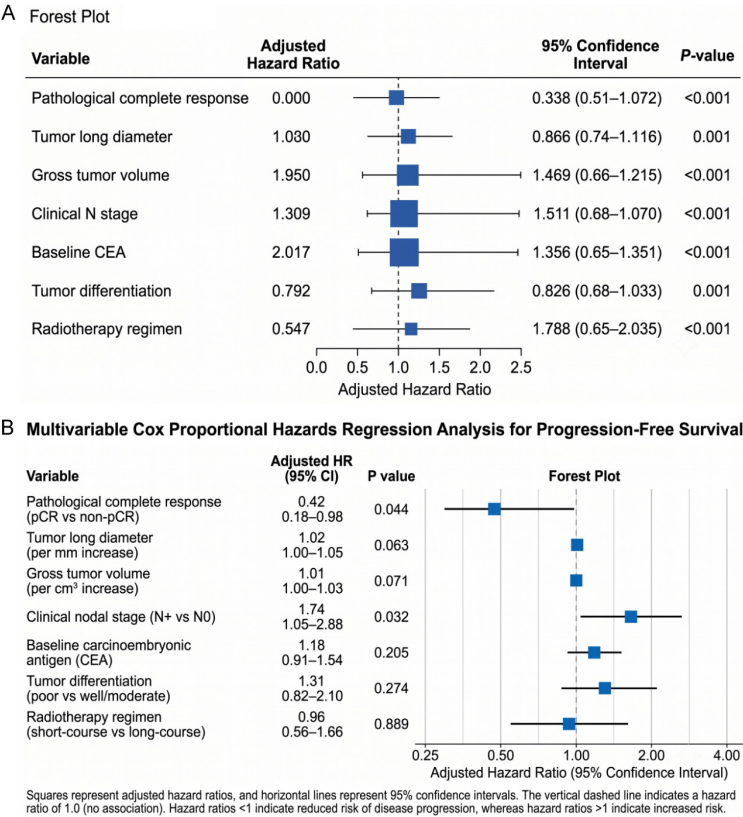
Pretreatment MRI characteristics also demonstrated important associations with pathologic

response. Patients achieving pCR had significantly smaller baseline tumor size and gross tumor volume than those with residual disease, suggesting that pretreatment tumor burden influences response to neoadjuvant therapy. Smaller tumors are generally associated with improved oxygenation,

reduced intratumoral heterogeneity, and fewer radioresistant tumor cell populations, all of which may contribute to enhanced radiosensitivity. In contrast, larger tumors frequently exhibit hypoxia, genomic instability, and complex stromal interactions that have been associated with treatment resistance. These findings are consistent with previous reports demonstrating the prognostic value of MRI-derived tumor volume in predicting treatment response [22-26].

Although clinical T stage was comparable between the two groups, MRI-defined nodal status differed significantly, suggesting that nodal disease burden may provide additional prognostic information beyond primary tumor stage alone. Incorporation of quantitative MRI-derived tumor burden together with nodal characteristics into future predictive models may improve patient stratification before treatment and facilitate individualized therapeutic decision-making.

One of the most clinically relevant findings of this study was the persistence of post-treatment MRI abnormalities despite complete pathologic response. Tumor-bed fibrosis, residual



**Figure 4.** A. Forest plot of Cox regression analysis. B. Multivariable Cox proportional hazards regression analysis for progression-free survival. Note: Forest plot showing hazard ratios (HRs) and 95% confidence intervals (CIs) derived from multivariable Cox proportional hazards regression analysis for progression-free survival. Variables included pathological complete response, baseline tumor long diameter, gross tumor volume, clinical nodal stage, baseline carcinoembryonic antigen level, tumor differentiation, and radiotherapy regimen.

diffusion-weighted imaging (DWI) hyperintensity, fibrotic scar formation, submucosal edema, and mucin lake-like changes remained common among patients with pCR. These findings likely represent treatment-induced tissue remodeling rather than persistent viable malignancy. Radiotherapy induces fibrosis, inflammation, vascular remodeling, edema, and extracellular matrix reorganization, all of which may produce imaging appearances that resemble residual tumor despite complete pathologic eradication [28–30].

Residual DWI hyperintensity deserves particular attention because diffusion restriction is traditionally regarded as a marker of high cellular density and residual malignancy. In our cohort, however, residual DWI abnormalities were frequently observed even among patients with pathologic complete response. These find-

ings suggest that treatment-related inflammatory responses, mucosal regeneration, fibrosis, and tissue repair may contribute to persistent diffusion abnormalities after successful treatment. Consequently, interpretation of DWI findings in isolation may increase the risk of overestimating residual disease and influence unnecessary surgical intervention or inappropriate exclusion from organ-preservation strategies.

Similarly, tumor-bed fibrosis was observed in nearly all patients with pCR. Although low T2-signal fibrosis is generally regarded as a favorable imaging feature following neoadjuvant therapy, differentiating dense fibrosis from microscopic residual tumor remains challenging using conventional MRI alone. The substantial overlap between post-treatment fibrosis and residual tumor limits diagnostic confidence and highlights the need for more objective imaging biomarkers. Future studies should investigate quantitative MRI parameters, including appar-

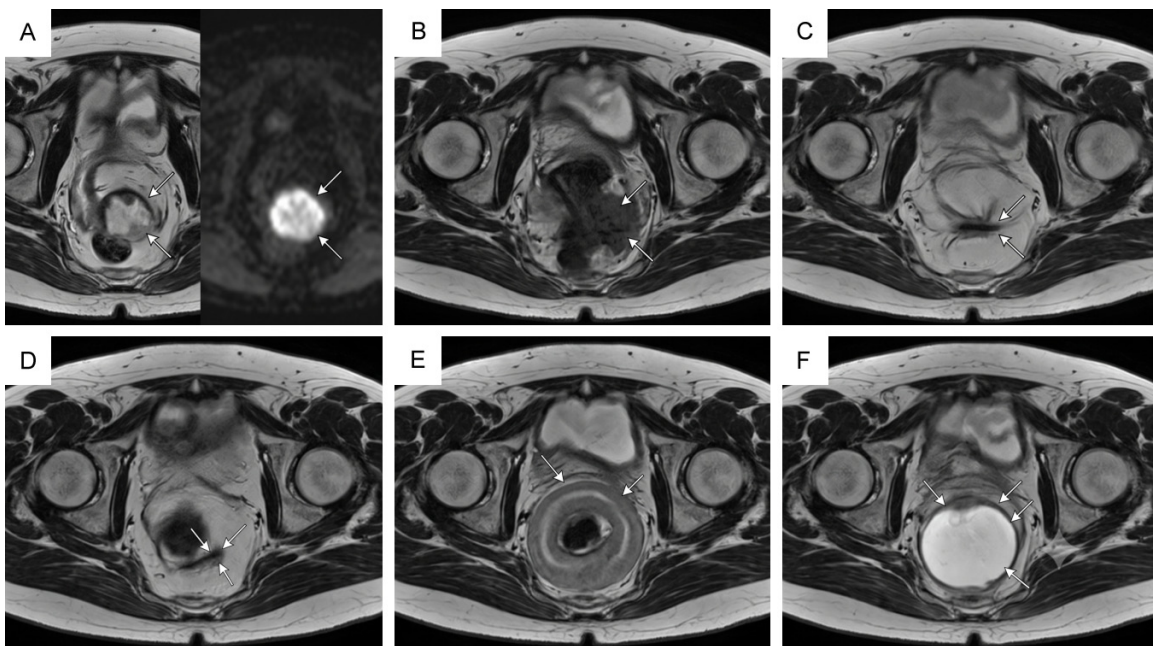
ent diffusion coefficient (ADC) measurements, radiomic signatures, multiparametric MRI, and artificial intelligence-assisted image analysis to improve response assessment following neoadjuvant treatment [32–34].

Importantly, the persistence of qualitative MRI abnormalities did not necessarily correspond to inferior oncologic outcomes among patients achieving pCR. These observations emphasize that conventional MRI findings should not be interpreted independently but rather integrated with clinical examination, endoscopic findings, pathological assessment, laboratory investigations, and serial imaging during multidisciplinary decision-making. Such an integrated approach may improve treatment selection while reducing the risk of overtreatment in patients with favorable biological response [35–37].

**Table 10.** Univariable Cox regression analysis of individual post-radiotherapy MRI response patterns for progression-free survival and overall survival within the pCR cohort (n = 48)

| MRI Response Pattern        | Progression-Free Survival<br>HR (95% CI) | P value | Overall Survival HR<br>(95% CI) | P value |
|-----------------------------|------------------------------------------|---------|---------------------------------|---------|
| Residual DWI hyperintensity | 1.18 (0.39-3.59)                         | 0.771   | 1.09 (0.18-6.43)                | 0.923   |
| Tumor-bed fibrosis          | 0.94 (0.11-8.08)                         | 0.956   | 0.88 (0.09-8.27)                | 0.911   |
| Fibrotic scar formation     | 0.88 (0.29-2.66)                         | 0.824   | 0.81 (0.14-4.71)                | 0.817   |
| Submucosal edema            | 1.14 (0.37-3.46)                         | 0.822   | 1.02 (0.18-5.91)                | 0.983   |
| Mucin-lake-like changes     | 1.42 (0.44-4.56)                         | 0.553   | 1.36 (0.24-7.82)                | 0.727   |

Abbreviations: HR, hazard ratio; CI, confidence interval; DWI, diffusion-weighted imaging; PFS, progression-free survival; OS, overall survival. Footnote: Hazard ratios were estimated using univariable Cox proportional hazards regression within the pathologic complete response cohort. None of the evaluated post-radiotherapy MRI response patterns demonstrated a significant association with progression-free survival or overall survival.



**Figure 5.** Representative post-radiotherapy pelvic magnetic resonance imaging (MRI) findings in patients with pathologic complete response. Note: Representative images demonstrate (A) residual diffusion-weighted imaging (DWI) hyperintensity, (B) tumor-bed fibrosis characterized by low T2-weighted signal intensity, (C, D) fibrotic scar formation replacing the original tumor site, (E) submucosal edema within the treated rectal wall, and (F) mucin-lake-like changes characterized by high T2-weighted signal intensity. Despite these persistent imaging abnormalities, pathologic examination confirmed complete tumor eradication (ypTON0).

The present study had several important clinical implications. First, our findings reinforce the prognostic significance of pathologic complete response following neoadjuvant therapy. Second, the frequent persistence of MRI abnormalities despite complete pathologic response highlights the limitations of relying exclusively on conventional MRI when assessing treatment response. Third, combining radiological, pathologic, and clinical information may improve patient selection for organ-preservation

strategies and individualized surveillance protocols. Finally, these findings provide additional evidence supporting multidisciplinary interpretation of post-treatment imaging in routine clinical practice.

This study has several strengths. It included a well-characterized consecutive cohort of patients treated within a standardized institutional pathway, incorporated comprehensive radiologic, pathologic, and survival data, and

evaluated multiple post-treatment MRI response patterns in relation to long-term oncologic outcome.

Several limitations should be acknowledged. First, the retrospective single-center design introduced the potential for selection bias, information bias, and residual confounding. Second, although the overall cohort was of moderate size, the relatively small number of patients achieving pCR and the limited number of survival events reduced the statistical power of subgroup analyses. Third, standardized quantitative MRI biomarkers, including ADC measurements, volumetric response assessment, and radiomic features, were not consistently available because of the retrospective nature of the study. Fourth, although multivariable analyses were performed to adjust for clinically relevant covariates, unmeasured confounding could not be completely excluded. Finally, the findings require external validation in larger prospective multicenter cohorts before widespread clinical application.

Future prospective studies should incorporate standardized MRI acquisition protocols, quantitative imaging biomarkers, radiomics, artificial intelligence-assisted image interpretation, and external validation cohorts to improve the non-invasive prediction of pathologic complete response. Integration of imaging biomarkers with molecular and clinicopathologic characteristics may further enhance personalized treatment strategies and optimize patient selection for organ-preservation approaches.

## Conclusion

In this retrospective cohort study, pathologic complete response following neoadjuvant radiotherapy was associated with a lower recurrence rate in patients with locally advanced rectal adenocarcinoma. Patients achieving pCR demonstrated lower pretreatment MRI-defined tumor burden and experienced reduced recurrence rates compared to those with residual disease. Despite complete pathologic tumor eradication, persistent post-radiotherapy MRI abnormalities including residual diffusion-weighted imaging hyperintensity, tumor-bed fibrosis, fibrotic scar formation, and submucosal edema were frequently observed. These findings suggest that conventional post-treatment MRI abnormalities often represent treat-

ment-related tissue remodeling rather than residual viable malignancy. Consequently, post-treatment MRI should be interpreted within a multidisciplinary framework that integrates radiological findings with pathologic assessment, clinical evaluation, and longitudinal follow-up. Future prospective multicenter studies incorporating quantitative MRI biomarkers, radiomics, and artificial intelligence-assisted image analysis are warranted to improve the accuracy of response assessment and support individualized treatment strategies in rectal cancer.

## Disclosure of conflict of interest

None.

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