

MINISTRY OF EDUCATION

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HANOI MEDICAL UNIVERSITY



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**RESULTS OF INDUCTION FOLFIRINOX AND
PREOPERATIVE RADIOTHERAPY COMBINED WITH
CAPECITABINE FOR LOCALLY ADVANCED
LOWER-MIDDLE RECTAL CANCER**

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SUMMARY OF THE DOCTORAL THESIS IN MEDICINE

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The thesis may be consulted at:

- National Library
- Hanoi Medical University Library

LIST OF PUBLISHED WORKS RELATED TO THE THESIS

1. Nguyen Van Hung, Nguyen Nhat Tan, Pham Duy Manh, Tran Trung Bach, Duong Thuy Linh, Pham Thi Hoan, Tran Ngoc Dung, Trinh Le Huy. Preliminary results of total neoadjuvant therapy in patients with locally advanced rectal cancer. *Journal of Medical Research*. 2024;185(12):44-51. doi:10.52852/tencyh.v185i12.2790
2. Nguyen HV, Trinh HL, Tran ND, et al. Total Neoadjuvant Therapy with Induction FOLFIRINOX and Concurrent Chemoradiation for Locally Advanced Lower-Middle Rectal Cancer: A retrospective study in Vietnam. *Technology in Cancer Research & Treatment*. 2025; 24: 153303 38251398075.
3. Nguyen Van Hung, Duong Khac Duc, Tran Ngoc Dung, Trinh Le Huy. Treatment response and adverse events of induction chemotherapy and preoperative chemoradiation in locally advanced mid-lower rectal cancer. *Journal of Medical Research*. 2026; 201(4):399-407. doi:10.52852/tencyh.v201i4.5120

INTRODUCTION OF THE THESIS

1. Rationale of the thesis

Locally advanced lower-middle rectal cancer requires multimodality treatment, in which surgery combined with preoperative chemoradiotherapy and adjuvant chemotherapy had previously been the standard strategy. However, rates of locoregional recurrence and distant metastasis remain substantial, prompting the development of more effective treatment strategies. Total neoadjuvant therapy (TNT), in which both systemic chemotherapy and radiotherapy are moved to the preoperative setting, has shown the ability to improve pathological complete response, reduce distant recurrence, and prolong survival compared with preoperative chemoradiotherapy alone. Among TNT regimens, induction FOLFIRINOX combined with chemoradiotherapy using capecitabine before surgery is a promising approach, with favorable pCR rates and survival outcomes in recent studies. Nevertheless, the role of this regimen in patients with locally advanced mid–low rectal cancer has not been fully standardized, and data on its feasibility, efficacy, and safety in real-world clinical practice in Vietnam remain limited. From these considerations, we conducted the study: “Results of induction FOLFIRINOX and preoperative radiotherapy combined with capecitabine for locally advanced lower-middle rectal cancer” with the following two objectives:

1. *To evaluate the treatment outcomes of induction FOLFIRINOX and preoperative radiotherapy combined with capecitabine for locally advanced lower-middle rectal cancer.*
2. *To assess adverse effects of the regimen in the study population.*

2. New contributions of the thesis

The thesis has the following notable new contributions:

- Total neoadjuvant therapy using induction FOLFIRINOX and preoperative radiotherapy combined with capecitabine in patients with locally advanced mid–low rectal cancer achieved a complete endoscopic response rate of 21.2% and a pathological complete response rate of 28.2%. Among the examined factors, post-treatment endoscopic tumor status was significantly associated with the likelihood of achieving pCR after TNT.
- Disease-free survival outcomes were favorable, with 3-year DFS of 91.1% and 5-year DFS of 87.3%. The NAR score, which evaluates treatment response, had prognostic significance for DFS, particularly at the threshold of <12.
- The regimen was well tolerated, with 91.8% of patients completing induction chemotherapy and 100% completing concurrent chemoradiotherapy. Toxicities were predominantly grade I–II, while grade $\geq$ III toxicities were uncommon.

3. Structure of the thesis

The thesis comprises 128 pages, including 2 pages of Introduction, 41 pages of Literature Review, 19 pages of Subjects and Methods, 31 pages of Results, 32 pages of Discussion, 2 pages of Conclusions, and 1 page of Recommendations. The dissertation contains 37 tables, 5 figures, and 12 charts, with 181 references.

The doctoral candidate has published 2 articles in reputable specialty journals, including 1 article in Journal of Medical Research (Vietnam) and one in English-language international journal.

CHAPTER 1: LITERATURE REVIEW

1.1. EPIDEMIOLOGY OF RECTAL CANCER

1.1.1. Global epidemiology of rectal cancer

Globally, rectal cancer is a common malignancy, ranking eighth in incidence and ninth in mortality, with 778,594 new cases and 339,370 deaths in 2024 according to GLOBOCAN.

1.1.2. Epidemiology of rectal cancer in Vietnam

In Vietnam, colorectal cancer ranks third among all cancers in both sexes. In men, colorectal cancer ranks second (after lung cancer), accounting for 14.7% of all new cancers in males, with an age-standardized incidence rate of 22.7/100,000. In women, it ranks third (after breast and thyroid cancers), accounting for 10.9% of all new cancers, with an age-standardized incidence rate of 14.1/100,000.

1.2. ANATOMICAL AND PATHOLOGICAL CHARACTERISTICS OF RECTAL CANCER

1.2.1. Low-mid rectal anatomy

The rectum is the terminal portion of the large intestine, extending from the sigmoid colon to the anus. It is commonly divided into three segments according to the distance from the anal verge: the lower rectum, <5 cm; the middle rectum, 5–10 cm; and the upper rectum, >10 cm.

1.2.2. Pathological classification

At present, colorectal cancer pathology is classified according to the 2019 World Health Organization (WHO) system.

1.2.3. Histological grade

Both the American Pathology Association and AJCC/UICC use a 4-grade classification for colorectal cancer based on gland formation: Grade 1: well differentiated (>95% gland formation), Grade 2: moderately differentiated (50–95% gland formation), Grade 3: poorly differentiated (<50% gland formation), Grade 4: undifferentiated (no gland formation).

Meanwhile, WHO recommends a grading system in which well and moderately differentiated tumors are grouped into low histological grade, while poorly differentiated and undifferentiated tumors are grouped into high histological grade. This classification is simpler while retaining prognostic value.

1.2.4. Tumor regression grade

Pathological response to radiotherapy, chemotherapy, or chemoradiotherapy before surgery is an important prognostic factor. This response is assessed by pathologists and recorded according to grading systems based on the postoperative specimen. Considerable evidence shows that pathological complete response is closely associated with better prognosis. In addition, the degree of response is also associated with improved outcomes.

1.3. DIAGNOSIS OF LOCALLY ADVANCED RECTAL CANCER

1.3.1. Rectal cancer staging according to AJCC 2017

At present, rectal cancer staging is still performed according to AJCC 8th edition, published in 2017. UICC TNM 9th edition was published in 2025 and took effect on January 1, 2026. However, in the official updates from UICC, colorectal cancer was not listed among the major sites with substantial revisions in this edition.

1.3.2. Role of endoscopy in the diagnosis and assessment of treatment response

Colonoscopy plays an important role in the diagnosis of rectal cancer by allowing direct visualization of the lesion, assessment of its location, morphology, and circumferential extent within the rectal lumen, as well as tissue biopsy for

histopathological confirmation. Complete colonoscopy also facilitates the detection of synchronous lesions in other segments of the colon and rectum.

After neoadjuvant treatment, endoscopy is important for assessing response at the primary tumor site. Endoscopic features suggestive of a complete response include disappearance of the tumor and replacement by a flat white scar, which may be accompanied by telangiectasia, with no residual nodularity or visible tumor. In contrast, persistent ulceration, irregular mucosa, or nodular lesions are associated with a higher likelihood of residual tumor.

1.3.3. Pre-treatment staging by magnetic resonance imaging

T stage is determined according to the depth of tumor invasion into the rectal wall. T1 indicates invasion limited to the mucosa and submucosa; T2 indicates invasion into the muscularis propria. The tumor is classified as T3 when it extends beyond the muscularis propria into the perirectal fat. T3 lesions are further subdivided into four categories according to the greatest depth of extension beyond the muscularis: T3a <1 mm, T3b 1–5 mm, T3c 5–15 mm, and T3d >15 mm. T4 is defined when the tumor invades the peritoneum (T4a) or invades adjacent pelvic organs or structures, including muscles (T4b). MRI also helps assess mesorectal fascia involvement (MRF – Mesorectal fascia) and extramural venous invasion (EMVI – Extramural venous invasion).

Compared with its accuracy in diagnosing tumor invasion, MRI is less accurate in assessing lymph node metastasis in rectal cancer. Node size is the most reliable parameter for predicting metastatic lymph nodes, with accuracy ranging from 43% to 85%. According to the 2016 consensus of the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), lymph nodes are considered metastatic on MRI if they meet one of the following criteria: (1) short-axis diameter ≥ 9 mm; (2) short-axis diameter 5–8 mm and ≥ 2 suspicious morphological features; (3) short-axis diameter <5 mm and 3 suspicious morphological features; (4) all mucinous nodes regardless of size. Suspicious morphological features include: round shape, irregular border, and heterogeneous signal intensity.

1.3.4. Assessment of tumor regression on MRI

Assessment of tumor regression grade (mrTRG) on MRI is important in determining the degree of response of rectal cancer after neoadjuvant treatment, thereby supporting subsequent treatment decisions such as radical surgery or watch-and-wait. However, assessment of mrTRG remains challenging in some cases. Distinguishing residual tumor from fibrosis and post-radiation changes may reduce MRI accuracy compared with pre-treatment evaluation.

1.4. TREATMENT MODALITIES FOR LOCALLY ADVANCED RECTAL CANCER

1.4.1. Surgical treatment of rectal cancer

In rectal cancer treatment, surgery is the most important modality. Total mesorectal excision has become the standard in surgical treatment of rectal cancer. The current trend is to maximize sphincter preservation in order to improve quality of life without compromising survival. Laparoscopic and robotic surgery are advances currently being applied at many surgical centers.

1.4.1.1. Distal resection margin

Preoperative concurrent chemoradiotherapy is commonly used for locally advanced rectal cancer, helping improve local control and increase sphincter preservation rates. Many studies have shown that, in low rectal cancers treated with preoperative chemoradiotherapy, a distal margin of 1 cm may be acceptable and may expand indications for sphincter-preserving surgery.

1.4.1.2. Circumferential resection margin

The circumferential resection margin is defined as the shortest distance from the primary tumor or mesorectal lymph node to the surgical margin, measured on the postoperative specimen. One of the main goals of surgery for low rectal cancer is to ensure a negative circumferential margin in order to prevent local recurrence. Achieving this requires accurate preoperative imaging assessment, preoperative chemoradiotherapy when indicated, and high-quality TME surgery.

1.4.1.3. Lateral pelvic lymph node dissection

The JCOG0212 trial (2017) was conducted to clarify the role of prophylactic lateral pelvic lymph node dissection in low rectal cancer. The results showed that although the trial did not demonstrate a disease-free survival benefit, encompassing both local and distant recurrence, for prophylactic lateral pelvic lymph node dissection, the group undergoing dissection had a lower rate of local recurrence.

1.4.1.4. Minimally invasive surgery

Laparoscopic surgery offers many advantages for patients, including faster recovery, better cosmetic outcomes, and improved postoperative quality of life. In 2003, the Da Vinci robot was first used in rectal cancer surgery for low anterior resection and abdominoperineal resection. A 2020 systematic review found that although robotic surgery had a longer operative time, it was associated with a lower conversion rate to open surgery, faster bowel function recovery, lower complication rates, and better access to technically difficult operative fields compared with laparoscopic surgery.

1.4.1.5. Organ preservation after preoperative treatment

Local excision

Transanal local excision is performed for early-stage rectal tumors, whereas TME remains the usual indication for locally advanced disease. The GRECCAR 2 trial (2020) concluded that local excision may be an appropriate option for a subgroup of patients with low rectal cancer cT2–3 who show a good response to preoperative chemoradiotherapy.

Active surveillance strategy

With advances in treatment modalities, nonoperative management is now an option for selected patients, particularly those with a complete clinical response after total neoadjuvant treatment, those with contraindications to surgery, or those in whom surgery would severely impair quality of life. Patients must be followed closely after neoadjuvant treatment so that recurrences can be detected and treated promptly without compromising survival.

1.4.2. Radiotherapy for rectal cancer

Radiotherapy is an important component of multimodal treatment for locally advanced rectal cancer, particularly for mid- and low-rectal tumors with a high risk of local recurrence. The primary aim of preoperative pelvic radiotherapy is to control the primary tumor and regional nodal areas at risk, reduce the risk of locoregional recurrence, and facilitate curative resection. The addition of concurrent chemotherapy to radiotherapy improves local control and tumor response compared with radiotherapy alone.

Within contemporary total neoadjuvant therapy (TNT) strategies, radiotherapy continues to play a key role in locoregional disease control, while systemic chemotherapy is administered before surgery to enhance systemic disease control. The two most extensively studied radiotherapy approaches are short-course radiotherapy, typically delivered as 25 Gy in 5 fractions, and long-course chemoradiotherapy, usually delivered to a total dose of approximately 45–50.4 Gy with concurrent fluoropyrimidine. The choice between these approaches depends on tumor risk characteristics, the need for tumor downstaging, and the sequencing of systemic therapy.

1.4.2.1. Preoperative and postoperative radiotherapy

One of the major paradigm shifts in rectal cancer radiotherapy has been the transition from postoperative to preoperative radiotherapy. Preoperative radiotherapy can reduce tumor size and thereby facilitate surgery. Tumor downsizing may also increase the likelihood of sphincter-preserving surgery in low rectal cancer. Preoperative radiotherapy has the advantage that tumor cells are better oxygenated because the vascular supply has not yet been disrupted by surgery, making them more radiosensitive. In addition, preoperative radiotherapy lowers the risk of radiation enteritis because the small bowel has not yet adhered to the postoperative pelvic field.

1.4.2.2. Short-course and long-course radiotherapy

In many countries, especially in some European countries, short-course radiotherapy has been accepted as a standard preoperative option for resectable rectal adenocarcinoma. However, at many other centers, such as in the United States, long-course chemoradiotherapy remains the preferred approach, particularly in patients with bulky tumors, T4 disease, or a high risk of a positive circumferential margin. In clinical practice, short-course radiotherapy is often considered for selected cases, such as patients requiring a shorter preoperative treatment interval, those unable to tolerate a long-course regimen, or those who need early transition to systemic therapy, particularly in the setting of metastatic disease.

1.4.2.3. Radiotherapy techniques

Initially, radiotherapy techniques for rectal cancer used simple two-dimensional planning based on pelvic X-ray images. The advent of CT simulation-based planning allowed more accurate identification and delineation of target volumes in three-dimensional space. However, many pelvic nodal regions have concave shapes, and 3D-CRT cannot easily spare normal tissues located between these target volumes. In principle, IMRT and VMAT can improve tolerability and permit dose escalation without increasing late toxicity because they provide better sparing of organs at risk. However, to date, there is insufficient evidence from clinical trials to replace 3D-CRT in routine practice. Therefore, according to current recommendations, 3D-CRT remains the standard technique, while IMRT/VMAT are indicated in selected cases.

1.4.2.4. New research directions in rectal cancer radiotherapy

New research directions in rectal cancer radiotherapy include contact X-ray brachytherapy (CXB), proton therapy, radiomics, and artificial intelligence (AI) in personalized radiotherapy. These are all novel and promising approaches in rectal cancer radiotherapy; however, further clinical trials are still needed to clarify their efficacy and safety compared with current standard treatments.

1.4.3. Systemic treatment

1.4.3.1. Concurrent chemoradiotherapy

Trials such as FFCD 9203 (2006) and EORTC (2005) compared long-course chemoradiotherapy with radiotherapy alone and showed that preoperative concurrent chemoradiotherapy improved tumor downstaging and reduced local recurrence compared with radiotherapy alone. Capecitabine is an oral fluoropyrimidine derivative and has been shown to be equivalent in efficacy to infusional 5-FU in concurrent chemoradiotherapy.

1.4.3.2. Adjuvant chemotherapy

Adjuvant chemotherapy after curative surgery for rectal cancer has been shown to reduce the risks of recurrence and death and therefore has become a standard component of treatment in patients who did not receive neoadjuvant therapy before surgery. However, in patients who have already received preoperative chemoradiotherapy, the benefit of adjuvant chemotherapy remains unclear. Some retrospective analyses suggest limited benefit, especially in patients who achieve pathological complete response. Nevertheless,

oxaliplatin-containing regimens, such as FOLFOX in the ADORE trial, have shown improved disease-free survival compared with 5-FU/leucovorin alone.

1.4.3.3. Some new treatment directions in locally advanced mid–low rectal cancer

Recently, immunotherapy has shown very promising efficacy in patients with locally advanced rectal cancer harboring mismatch repair deficiency (dMMR). In contrast, the addition of targeted agents such as bevacizumab or cetuximab in locally advanced rectal cancer has not yet demonstrated superior benefit compared with current standard treatment.

1.5. TOTAL NEOADJUVANT THERAPY IN LOCALLY ADVANCED RECTAL CANCER

1.5.1. Trends and outcomes of total neoadjuvant therapy

Total neoadjuvant therapy has been proposed for its potential to allow earlier access to systemic treatment, eliminate micrometastatic disease, improve tolerance to chemotherapy before major surgery, and achieve better tumor downstaging.

The RAPIDO trial (2020) compared short-course radiotherapy plus chemotherapy before surgery versus preoperative chemoradiotherapy followed by surgery and adjuvant chemotherapy in high-risk locally advanced rectal cancer. The study showed a higher pathological complete response rate in the intervention group than in the standard-treatment group (28% vs 14%). However, in the 2023 update, the local recurrence rate in the intervention arm was higher than that in the standard-treatment arm.

The PRODIGE study (2021), a phase III, open-label, multicenter, randomized trial in patients with cT3–T4 M0 rectal cancer, compared induction FOLFIRINOX plus chemoradiotherapy plus surgery plus adjuvant chemotherapy with chemoradiotherapy plus surgery plus adjuvant chemotherapy. The study showed that the intervention group had a 3-year DFS of 76%, significantly higher than the 69% observed in the control group ($p=0.034$). The pCR rate was 28% in the intervention group versus 12% in the control group. The 2024 update showed a 7-year OS of 81.9% in the TNT group versus 76.1% in the chemoradiotherapy group.

A 2024 systematic review and meta-analysis comparing triplet TNT regimens—induction FOLFIRINOX followed by long-course chemoradiotherapy and surgery—with doublet TNT regimens—oxaliplatin–fluoropyrimidine (CAPOX/FOLFOX) followed by chemoradiotherapy and surgery—showed superior efficacy of the triplet regimen and a trend toward better outcomes than chemoradiotherapy alone, with 5-year OS of 86.8% versus 74.7% and 79.6%, respectively, and corresponding 5-year DFS rates of 73.1% versus 61.7% and 65.1%.

1.5.2. Adverse effects of total neoadjuvant therapy

The RAPIDO study (2020) showed that TNT using the short-course radiotherapy and preoperative chemotherapy model may increase acute toxicities, particularly diarrhea and neurotoxicity, although these remained at an acceptable level.

The PRODIGE study (2021) showed that the TNT strategy with induction FOLFIRINOX was associated with substantial hematologic and gastrointestinal toxicities, but overall these remained within a manageable range. The treatment completion rate reached 92%.

The systematic pooled analysis by Moretto et al. (2024) showed that induction treatment with FOLFIRINOX, compared with an oxaliplatin-based doublet regimen, was associated with higher toxicity, mainly involving the hematologic and gastrointestinal systems. The triplet regimen was associated with a markedly higher rate of severe neutropenia than the doublet regimen (17% vs 1%, $p<0.0001$), while severe

nausea/vomiting was also more frequent (11% vs 3%, $p=0.02$). Therefore, careful patient selection and intensive supportive monitoring are required in clinical practice.

1.5.3. Research on Total Neoadjuvant Therapy in Vietnam

In Vietnam, TNT for rectal cancer has also been implemented and investigated in recent years.

Nguyen Hai Hoang and colleagues (2024) conducted a study involving 73 patients treated at the 108 Military Central Hospital and Nghe An Oncology Hospital. The treatment protocol consisted of chemoradiotherapy, consolidation chemotherapy with mFOLFOX6 or CAPEOX, followed by surgery. The pCR rate was 30.1%. Sphincter-preserving surgery was performed in 75.3% of patients overall and in 46.7% of those with low rectal cancer.

Nguyen Thi Ngoc Ha and colleagues (2025) studied 71 patients with stage II–III rectal cancer who received short-course radiotherapy at a dose of 25 Gy in five fractions, consolidation chemotherapy with CAPEOX or mFOLFOX6, and subsequent surgery at Hanoi Oncology Hospital, K Hospital, and the 108 Military Central Hospital. Overall, 94.4% of patients completed the planned chemotherapy regimen, and the pCR rate was 33.3%. The overall sphincter preservation rate was 79.7%, increasing to 57.1% among patients with low rectal cancer. The most common acute toxicities were thrombocytopenia and elevated liver enzyme levels, which were predominantly grade 1–2.

A report from National Cancer Hospital (2026) included 148 patients with stage II–III middle or low rectal cancer who underwent TNT using chemotherapy regimens combined with either short-course radiotherapy or long-course chemoradiotherapy. Tumor downstaging was observed in 68.9% of patients, the pCR rate was 25.7%, and the sphincter preservation rate was 71.6%. The most common grade 3–4 toxicities were neutropenia, occurring in 8.1% of patients, and diarrhea, occurring in 4.1%. Multivariable analysis showed that an earlier tumor stage and the use of a triplet chemotherapy regimen were associated with a higher likelihood of achieving pCR.

In Vietnam, triplet chemotherapy regimens have been used in colorectal cancer, mainly in metastatic disease. More recently, induction FOLFIRINOX and concurrent chemoradiotherapy with capecitabine before surgery have gradually been introduced at several centers, showing promising efficacy and feasibility. However, Vietnamese data on the efficacy and toxicity of this regimen remain limited. To improve the quality of treatment for locally advanced rectal cancer in Vietnam, our study focused on applying a triplet induction chemotherapy regimen combined with concurrent chemoradiotherapy and surgery in Vietnamese patients in order to characterize response patterns and the toxicity profile in this population.

CHAPTER 2: STUDY SUBJECTS AND METHODS

2.1. STUDY SUBJECTS

Patients with pathologically confirmed locally advanced mid and low rectal cancer who were treated with induction chemotherapy and concurrent chemoradiotherapy before surgery and met the following inclusion and exclusion criteria were enrolled.

2.1.1. Inclusion criteria

Patients diagnosed with mid or low rectal cancer meeting the following criteria were included: (1) Histopathological diagnosis of rectal adenocarcinoma. (2) The lower border of the tumor located ≤ 10 cm from the anal verge. (3) Disease stage cT3, T4 M0 and/or cN+ according to AJCC 8th edition, 2017. (4) Age 18–75 years. (5) Treatment-naïve patients. (6) Good general condition: ECOG performance status 0–1. (7) Adequate bone marrow, liver, and renal function for FOLFIRINOX chemotherapy and chemoradiation with capecitabine. (8) No severe acute or chronic comorbid illness.

2.1.2. Exclusion criteria

(1) Patients with another concomitant malignancy. (2) Patients who had previously received cancer treatment. (3) Contraindication to combination chemotherapy. (4) Patients who did not agree to participate or did not comply fully with treatment and follow-up according to the study design.

2.2. METHODS

2.2.1. Study design

A descriptive longitudinal study without a control group.

2.2.2. Sample size

Sample size was calculated according to the formula: $n = Z_{(1-\alpha/2)}^2 \frac{p(1-p)}{(p.\epsilon)^2}$

N: sample size. α : significance level = 0.05 (95% confidence interval). Z: value corresponding to $\alpha = 0.05$ ($Z = 1.96$). p: 3-year disease-free survival. According to Kong's meta-analysis, this rate was 70.6%. ϵ : relative precision, chosen as 0.15.

The minimum required sample size was 71. The study enrolled 85 patients conveniently.

2.2.3. Study sites and study period

Study sites: The study was conducted at Hanoi Medical University Hospital, Military Hospital 103, and K Hospital.

The study included 85 patients, of whom 75 were recorded at Hanoi Medical University Hospital and Military Hospital 103; these patients received chemotherapy and surgery at Hanoi Medical University Hospital and radiotherapy at Military Hospital 103. The remaining 10 patients were recorded at K Hospital, where the entire course of treatment and follow-up was performed.

Study period: Data were collected from January 2019 to December 2025. This period included patient enrollment, collection of clinical, paraclinical, treatment, and follow-up data, and completion of data recording for analysis. December 2025 was the study database lock date. The shortest follow-up duration was 15.3 months and the longest was 70.2 months.

2.2.4. Research equipment and materials

A multifunctional linear accelerator (LINAC) system and CT simulator.

MONACO and XiO treatment planning systems.

Magnetic resonance imaging (MRI) and computed tomography (CT) scanners.

Simulation marking devices, including lead tape, lead wires, and tattoo ink.

Chemotherapeutic agents, including 5-fluorouracil (5-FU), oxaliplatin, leucovorin, irinotecan, and capecitabine, together with supportive medications and other equipment required for chemotherapy administration.

2.2.5. Study variables and indicators

* **Endoscopic response assessment:** Patients underwent endoscopy 4–6 weeks after completion of treatment. Complete endoscopic response was defined as the absence of residual tumor, with possible white scar, slight indentation, or stellate telangiectasia, without persistent ulceration or abnormal neovascularization.

* **MRI response assessment:** Patients underwent MRI 4–6 weeks after completion of treatment to assess response.

* **Pathological response assessment according to the Mandard TRG system:** Based mainly on the ratio of necrotic/fibrotic tissue (replacement of tumor tissue by fibrosis) relative to the amount of viable residual tumor cells.

* **Neoadjuvant rectal score (NAR):** $NAR = (5pN - 3(cT - pT) + 12)^2 / 9.61$; where cT belongs to {1, 2, 3, 4}, pT belongs to {0, 1, 2, 3, 4}, and pN belongs to {0, 1, 2}. The

constant 12 ensures that the summed score inside the brackets is always non-negative. The constant 9.61 in the denominator ensures that the final score ranges from 0 to 100.

* ***Disease-free survival (DFS)***: the time from initiation of treatment to local recurrence, distant metastasis, or death from any cause.

2.2.6. Study procedures

Patients who met all study criteria were enrolled. Each patient had a standardized study record form completed. Data were collected using a predesigned case report form. The participating centers were equipped with diagnostic and treatment facilities that met oncology specialty standards. Pretreatment staging, radiotherapy planning, surgery, and pathological assessment were performed according to the standardized study protocol, as follows:

- Step 1: Patient selection and pre-treatment evaluation
- Step 2: Induction chemotherapy with the FOLFIRINOX regimen
- Step 3: Response assessment of adverse events of induction chemotherapy
- Step 4: Concurrent chemoradiotherapy
- Step 5: Response assessment of adverse events of concurrent CRT
- Step 6: Surgical treatment
- Step 7: Adjuvant chemotherapy
- Step 8: Post-treatment follow-up

2.2.7. Data analysis

Descriptive analysis used means, standard deviations, medians, and minimum and maximum values. Comparisons of mean values used the t-test and Mann–Whitney U test. Associations between response and categorical variables were analyzed using the chi-square test or Fisher’s exact test. Kaplan–Meier curves were used to estimate disease-free survival. The log-rank test and logistic regression analysis were used to determine associated factors. A p value <0.05 was considered statistically significant. R software was used for data analysis and chart plotting.

2.2.8. Bias and bias control

Controlled sources of bias included: selection bias, data monitoring and checking, and loss to follow-up bias.

2.2.9. Research ethics

All patient information collected was kept confidential and used solely for research purposes. The study was approved by the Institutional Review Board for Biomedical Research of Hanoi Medical University (IRB – VN01001), approval No. 908/GCN-HĐĐĐNCYSH-ĐHYHN dated May 4, 2023.

CHAPTER 3: RESULTS

The study included 85 patients with locally advanced mid-to-low rectal cancer who received induction FOLFIRINOX chemotherapy followed by preoperative chemoradiotherapy with concurrent capecitabine at Hanoi Medical University Hospital, Military Hospital 103, and National Cancer Hospital between January 2019 and December 2025. The results were as follows:

3.1. CHARACTERISTICS OF THE STUDY POPULATION

3.1.1. Age, sex, and performance status: The mean age of the patients was 55.7 years, with a median age of 58 years; the youngest patient was 23 years old and the oldest was 73. Most participants were 40–60 years old (54.1%), followed by those older than 60 years (38.8%), whereas only 6 patients were under 40 years of age (7.1%). The study population was predominantly male, with 61 men (71.8%) and 24 women (28.2%), giving a male-to-female ratio of 2.5. All patients had good performance status (ECOG 0–1), and most had ECOG 0 before treatment.

3.1.2. Tumor characteristics on rectal endoscopy: On endoscopy, the most common tumor morphology was ulceroinfiltrative/exophytic-ulcerative, followed by exophytic tumors, whereas purely ulcerative tumors were less frequent at only 2.35%, and no infiltrative-type lesion was recorded. Tumor location was determined by the distance from the lower border of the tumor to the anal verge. Mid-rectal tumors were more common than low-rectal tumors in the study population. On colonoscopy, most tumors involved three-quarters of the rectal circumference, followed by half of the circumference. Tumors occupying the entire lumen were less common, accounting for approximately 15.3%, and those occupying one-quarter of the circumference were the least frequent (7.0%).

3.1.3. Baseline clinical characteristics: The most common presenting symptom before treatment was the passage of blood and mucus in the stool, reported in 84.7% of patients. This was followed by abdominal pain (36.5%), diarrhea (20.0%), altered bowel habits (18.8%), changes in stool caliber (17.6%), and constipation (4.7%). No patient presented with a self-palpable abdominal mass. Among systemic symptoms, weight loss was the most common, occurring in 76.5% of patients, followed by fatigue (44.7%) and anemia (5.9%).

3.1.4. Histopathological characteristics: Most tumors were moderately differentiated adenocarcinomas (91.8%), whereas poorly differentiated tumors were seen in only 6 patients (7.0%). No well-differentiated tumors were observed, and only 1 patient had mucinous histology (1.2%).

3.1.5. Tumor characteristics on pelvic MRI: Most patients had stage III disease (96.5%), with T3 tumors predominating (76.5%) and N2 nodal disease present in most cases (69.4%); only 3.5% had no nodal metastasis (N0). Mean tumor length on MRI was 4.23 ± 1.33 cm, ranging from 2 to 11 cm. Most tumors were longer than 4 cm. The proportions of patients with MRF-positive and EMVI-positive tumors on pretreatment MRI were 38.8% and 28.2%, respectively.

3.2. TREATMENT OUTCOMES OF INDUCTION FOLFIRINOX AND PREOPERATIVE CHEMORADIOTHERAPY WITH CAPECITABINE

3.2.1. MRI response: Before treatment, all patients had T3–T4 tumors (100%, 85 patients). After total neoadjuvant treatment, MRI before surgery showed that this proportion decreased to 78.8%, and the difference was statistically significant ($p < 0.001$). Before TNT, 69.4% of patients had N2 nodal disease; after treatment, the proportion of N2 disease decreased markedly to 23.5%, also with statistical significance ($p < 0.001$).

3.2.2. Endoscopic response: In this study, the proportion of patients with no visible residual tumor on endoscopy was 21.2% (18 patients), whereas 78.8% (67 patients) still had visible tumor on endoscopy.

3.2.3. Surgical outcomes and pathological response after surgery

Among the 85 patients included in the study, after total neoadjuvant treatment, 100% of operated patients achieved an R0 resection margin; 73 patients underwent sphincter-preserving radical surgery (85.9%), while 12 patients underwent radical surgery sacrificing the sphincter (14.1%).

Table 3.1. Pathological response after surgery according to Mandard

Regression grade	Number of patients	Percentage (%)
TRG 1	24	28,2
TRG 2	23	27,1
TRG 3	22	25,9
TRG 4	13	15,3
TRG 5	3	3,5
Total	85	100

Comment: Pathological evaluation after surgery showed that 28.2% of patients achieved complete response (TRG 1), and 81.2% had pathological response after surgery. The rate of good pathological response (TRG 1 and TRG 2) was 55.3%, whereas poor response (TRG 3, TRG 4, and TRG 5) accounted for 44.7%.

Table 3.2. Pathological response of the primary tumor after surgery

Pretreatment T stage	Pathological T stage					T stage downstaging
	pT0	pT1	pT2	pT3	pT4	
cT3	19	5	21	19	1	69.2%
cT4	5	4	3	7	1	95.0%
Total	24	9	24	26	2	75.3%

Comment: After surgery, the majority of patients (75.3%) who underwent TNT showed tumor downstaging compared with pretreatment status.

Table 3.3. Pathological response of lymph nodes after surgery

Pretreatment N stage	Pathological N stage			N stage downstaging
	pN0	pN1	pN2	
cN0	3	0	0	
cN1	21	2	0	91.3%
cN2	52	4	3	94.9%
Total	76	6	3	90.6%

Comment: After surgery, as many as 90.6% of patients had nodal downstaging compared with pretreatment status, with statistical significance ($p < 0.001$).

Table 3.4. Post-TNT response score (NAR)

Neoadjuvant rectal score (NAR)	
Median	8.43
Mean	9.35 $\pm$ 10.6
Range	0 – 50.36
NAR <8 vs. NAR $\geq$8	
NAR <8	36 (42.4%)
NAR $\geq$ 8	49 (57.6%)
Total	85 (100%)
NAR <12 vs. NAR $\geq$12	
NAR <12	60 (70.6%)
NAR $\geq$ 12	25 (29.4%)
Total	85 (100%)

NAR: Neoadjuvant rectal score

Comment: The median NAR score was 8.43, with the highest value 50.36 and the lowest 0. High post-treatment NAR (≥ 8) predominated at 57.6%, whereas low NAR accounted for 42.4%.

3.2.4. Factors associated with pathological response after surgery

3.2.4.1. Association between age, sex, differentiation grade, and pathological response:

No statistically significant difference in age or sex was observed between the pathological complete response group and the non-complete response group ($p > 0.05$). However, there was a significant association between differentiation grade and pathological complete response, with poorly differentiated/mucinous tumors tending to achieve pCR more frequently than moderately differentiated tumors ($p = 0.001$).

3.2.4.2. Association between pretreatment T stage, N stage, and pathological response:

In our study, no statistically significant differences were observed in T stage or nodal stage

between the pathological complete response group and the non-complete response group ($p>0.05$).

3.2.4.3. Association between selected endoscopic tumor features and pathological response: Pretreatment endoscopic appearance and distance from the tumor to the anal verge did not differ significantly between the complete and non-complete pathological response groups ($p>0.05$).

3.2.4.4. Association between selected MRI tumor features and pathological response: There were no statistically significant associations between pretreatment tumor length, MRF and EMVI status on MRI and pathological response ($p>0.05$).

3.2.4.5. Association between endoscopic response and pathological response after surgery

Table 3.5. Association between endoscopic response and pathological response after surgery

Characteristic	pCR n (%)	Non-pCR n (%)	p
Endoscopic response			
No residual tumor	15 (62.5)	3 (4.9)	< 0.001*
Residual tumor present	9 (37.5)	58 (95.1)	

**Fisher's exact test*

Comment: Endoscopic response was associated with pathological complete response; most patients with no residual tumor on endoscopy achieved pCR, and the difference was statistically significant ($p<0.001$).

3.2.4.6. Multivariable logistic regression analysis of factors associated with pathological response after surgery

Figure 3.1. Multivariable logistic regression analysis of factors associated with pathological response after surgery

Comment: No residual tumor on endoscopy after treatment was significantly associated with pCR ($p<0.001$). Other factors, including age group, pretreatment histologic differentiation, tumor length, pretreatment endoscopic tumor characteristics, pretreatment MRF status, and pretreatment EMVI status on MRI, were not significantly associated with pCR.

3.2.5. Survival

3.2.5.1. Disease-free survival \$

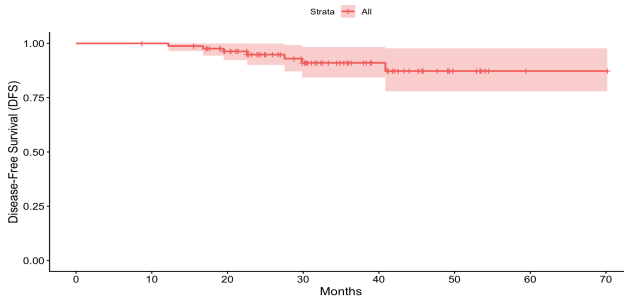


Figure 3.2. Disease-free survival

Comment: A total of 7 patients developed recurrence within 5 years after treatment. Estimated 3-year DFS was 91.1% (95% CI: 84.3–98.3%), and estimated 5-year DFS was 87.3% (95% CI: 77.9–97.8%).

3.2.5.2. Disease-free survival according to postoperative pathological response (TRG): DFS was higher in the group with good pathological response (TRG 1–2) than in the group with poor pathological response (TRG >2), but the difference was not statistically significant ($p=0.18$).

3.2.5.3. Disease-free survival according to pathological complete response (pCR): In the study population, DFS tended to be higher in the pCR group than in the non-pCR group, but the difference was not statistically significant ($p=0.53$).

3.2.5.4. Disease-free survival according to NAR score (cutoff 8): No statistically significant difference in DFS was observed between patients with NAR <8 and those with NAR ≥ 8 ($p=0.17$).

3.2.5.5. Disease-free survival according to NAR score (cutoff 12):

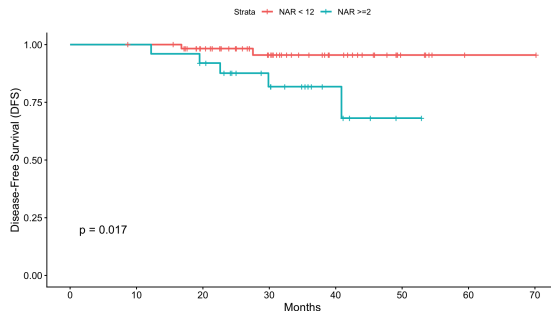


Figure 3.3. Disease-free survival according to NAR score (cutoff 12)

Comment: Patients with NAR <12 maintained an almost 100% DFS rate throughout follow-up, whereas the NAR ≥ 12 group experienced more events. DFS was longer in the NAR <12 group than in the NAR ≥ 12 group. The difference was statistically significant ($p=0.017$).

3.3. TOXICITIES OF THE REGIMEN

3.3.1. Adverse effects during induction chemotherapy

3.3.1.1. Hematologic toxicity of FOLFIRINOX by treatment cycle: Hematologic toxicity of induction chemotherapy was mainly grade I–II. By cycle, grade III–IV neutropenia

occurred in 4.0% of cycles, whereas grade II–IV leukopenia, thrombocytopenia, and anemia were each <2%.

3.3.1.2. Hematologic toxicity of FOLFIRINOX by patient: When toxicity was analyzed by patient, grade $\geq$ III toxicity was mainly neutropenia; other toxicities were uncommon.

3.3.1.3. Hepatic and renal toxicity of FOLFIRINOX by cycle: By cycle, hepatic and renal toxicities were mainly grade I. Grade III hepatic toxicity accounted for <1%.

3.3.1.4. Hepatic and renal toxicity of FOLFIRINOX by patient: Among the 85 patients, only 2 had grade III AST elevation. No grade III or higher renal toxicity was observed.

3.3.1.5. Gastrointestinal toxicity of FOLFIRINOX by cycle: Gastrointestinal and neurologic toxicities of induction chemotherapy were mainly grade I. Gastrointestinal toxicities were more common, including nausea, vomiting, diarrhea, and stomatitis, occurring in 18.0%, 6.0%, 10.6%, and 8.2% of cycles, respectively.

3.3.1.6. Gastrointestinal toxicity of FOLFIRINOX by patient: Nausea and vomiting grade $\geq$ III were observed in 4 patients in each toxicity.

3.3.1.7. Other toxicities of FOLFIRINOX by cycle: Hand-foot syndrome and peripheral neuropathy were only observed at grade I in the study group.

3.3.1.8. Other toxicities of FOLFIRINOX by patient: No patient experienced grade III or higher toxicities.

3.3.2. Adverse effects during concurrent chemoradiotherapy

3.3.2.1. Gastrointestinal toxicity of chemoradiation: The main gastrointestinal toxicity of concurrent chemoradiotherapy was proctitis, with 18 patients having grade I (21.2%), 9 patients grade II (10.6%), and 4 patients grade III (4.7%). No patient developed enteritis or bowel perforation.

3.3.2.2. Genitourinary toxicity of chemoradiation: Genitourinary toxicity was mainly grade I cystitis, occurring in 5.8% of patients. Only 1 patient developed vaginitis (1.2%).

3.3.2.3. Skin toxicity of chemoradiation: Skin toxicity of chemoradiotherapy was mainly grade I, occurring in 16.5% of patients. Four patients had grade II dermatitis (4.7%).

3.3.3. Treatment Compliance

Treatment-related toxicities were recorded in all 85 patients throughout the entire treatment course. Overall treatment completion was relatively high. Seventy-eight patients (91.8%) completed all 6 planned cycles of FOLFIRINOX. The treatment delay rate was 25.9%, and the dose reduction rate for induction chemotherapy was 9.4%. All patients completed concurrent chemoradiotherapy, corresponding to a completion rate of 100%.

CHAPTER 4: DISCUSSION

4.1. CHARACTERISTICS OF THE STUDY POPULATION

4.1.1. General characteristics

In our study, the mean age was 55.7 ± 10.3 years, ranging from 23 to 73 years. Most patients (54.1%) were between 40 and 60 years of age, followed by those older than 60 years (38.8%), while only 7.1% were younger than 40 years. Regarding sex, the disease occurred nearly 2.5 times more often in men than in women (71.8% vs 28.2%). International and domestic studies on total neoadjuvant treatment for rectal cancer have similarly reported mean ages of about 50–65 years and a male predominance.

Regarding pretreatment performance status, patients had good baseline condition, with ECOG 0 in 64.7% and ECOG 1 in 35.3%. This is important because FOLFIRINOX is an intensive chemotherapy regimen requiring good performance status to ensure tolerability, reduce the risk of treatment interruption, and maintain chemoradiotherapy on schedule.

4.1.2. Endoscopic tumor characteristics

Regarding tumor location, our study focused on mid–low rectal cancer, with mid-rectal tumors accounting for a higher proportion (57.6%) than low-rectal tumors (42.4%). Mid–low rectal tumors are the main indication for preoperative chemoradiotherapy in order to optimize sphincter preservation and reduce local recurrence. Low rectal tumors often require abdominoperineal resection and have a higher risk of local recurrence because it is more difficult to achieve a negative circumferential resection margin. The use of intensified preoperative FOLFIRINOX in this group is expected to downstage disease and thereby increase the chance of sphincter and anal preservation.

Our results showed that the predominant endoscopic morphology was ulcerative-exophytic, accounting for 83.5%, followed by exophytic type (11.8%), whereas ulcerative and infiltrative types accounted for only 2.4%. In terms of luminal extent, most tumors involved three-quarters of the rectal circumference (47.1%), followed by one-half (30.6%). Tumors involving the entire lumen were less common (15.3%), whereas those involving one-quarter of the circumference were least common (7.0%). Thus, the endoscopic features of the study group confirm a high tumor burden, supporting the need for an intensified treatment strategy.

4.1.3. Histopathological characteristics

Most tumors were moderately differentiated rectal adenocarcinomas, accounting for 91.8%, while poorly differentiated tumors accounted for only 7.1% (6 patients), mucinous histology was found in 1 patient (1.2%), and no well-differentiated tumors were recorded. Domestic and international studies likewise show that moderately differentiated adenocarcinoma predominates in rectal cancer, with rates ranging from 85% to 95% depending on the study sample. Although it accounted for only 7.1%, the poorly differentiated group is often associated with high proliferative activity and sometimes poorer response to conventional chemoradiotherapy.

4.1.4. Tumor and nodal characteristics on MRI

Most patients had stage III disease (96.5%), with T3 tumors predominating (76.5%); the majority had N2 nodal metastases (69.4%) or N1 disease (27.1%), while only 3.5% had N0 disease. The predominance of T3 indicates tumor extension through the muscular layer into perirectal fat, characteristic of locally advanced disease. Although T3 was the dominant T stage, approximately two-thirds of patients had N2 nodal metastasis before treatment. N2 disease is a strong independent adverse prognostic factor associated with worse DFS and OS, making systemic disease control a major priority. This supports the choice of an intensive multidrug chemotherapy regimen during the induction phase of TNT to eradicate micrometastatic disease early.

On pretreatment MRI, the rates of MRF positivity and EMVI positivity were 38.8% and 28.2%, respectively. The mesorectal fascia is the critical boundary in TME surgery, and MRF involvement on MRI predicts the likelihood of a positive circumferential resection margin after surgery. Five-year follow-up data from the MERCURY study of 374 rectal cancer patients showed that CRM positivity was the most important independent prognostic factor associated with increased risk of local recurrence and reduced DFS and OS. The fact that nearly one-third of patients had MRF-positive tumors indicates a high-risk group for local recurrence if treated with standard chemoradiotherapy alone. Therefore, intensifying chemotherapy with FOLFIRINOX before chemoradiotherapy is expected to produce stronger downstaging, optimize tumor shrinkage, convert MRF-positive to MRF-negative status, and increase the likelihood of achieving R0 resection.

In addition, most patients had tumors longer than 4 cm (50.6%). Although tumor length is commonly measured, some studies suggest that more important prognostic

factors include MRF and EMVI. A study by Gu (2018) found no significant difference in EMVI status between tumors ≥ 5 cm and < 5 cm. Shorter tumor length (< 4 cm) may be a favorable factor for achieving response, but it does not reduce overall risk in the presence of established high-risk features such as N2 disease, MRF positivity, and EMVI positivity. Overall, pelvic MRI is indispensable in evaluating stage and tumor characteristics in rectal cancer, especially T stage, nodal metastasis, MRF, and EMVI, thereby helping formulate appropriate treatment plans and improve surgical outcomes and prognosis.

4.2. TREATMENT OUTCOMES OF INDUCTION FOLFIRINOX AND PREOPERATIVE CHEMORADIOOTHERAPY WITH CAPECITABINE

Among the 85 patients in our study, after TNT, 100% of operated patients achieved R0 resection, including 73 patients who underwent sphincter-preserving radical surgery (85.9%) and 12 patients who underwent radical surgery sacrificing the sphincter (14.1%). This is a very favorable result, reflecting the local control efficacy of TNT combining induction FOLFIRINOX and preoperative chemoradiotherapy with capecitabine. The PRODIGE-23 trial reported an R0 rate of 95% after TNT, while RAPIDO reported 90%. In Asia, studies from Korea and Japan have also documented R0 rates ranging from over 90% to nearly 100%, depending on the degree of invasion into adjacent organs and surgical technique. Thus, the 100% R0 rate in our study suggests excellent response after TNT, allowing surgeons to perform precise dissections along the TME plane.

Another important goal of neoadjuvant therapy is to maximize sphincter preservation and improve quality of life. In our study, 85.9% of patients underwent sphincter-preserving radical surgery, a rate six times higher than that of sphincter-sacrificing surgery. This high rate of sphincter preservation is particularly meaningful because the study population mainly consisted of mid–low rectal cancers, which tend to involve the sphincter and often make it difficult to secure a safe distal margin. Our results were comparable to, and even trended higher than, sphincter preservation rates reported in other TNT trials. In Vietnam, early studies of TNT before rectal cancer surgery have reported very encouraging sphincter preservation rates, around 72–74%. However, in a meta-analysis by Kasi A et al. including 7 studies with 2,416 patients, no significant difference was found in sphincter-preserving surgery rates between the TNT group and the standard chemoradiotherapy group.

4.2.1. Treatment response

4.2.1.1. Endoscopic response

Our study recorded a complete endoscopic response rate of 21.2%. This response, defined as the absence of visible tumor or only a small fibrotic scar/ulcer, is an important clinical sign suggesting the possibility of pathological complete response afterward. This rate indicates a substantial clinical response, especially when compared with standard chemoradiotherapy regimens, which often achieve lower complete clinical response rates of around 10–15%.

It should be emphasized that endoscopic assessment of “no residual tumor” is not equivalent to pathological complete response. In domestic studies, clinical complete response has often been assessed at different time points. For example, one study at Military Central Hospital 108 reported a higher cCR rate when reassessment was performed at 18–24 weeks compared with 6–12 weeks (36.1% vs 11.1%). This suggests that the timing of endoscopic assessment is important: if performed too early after chemoradiotherapy, response may be underestimated, whereas later evaluation may reveal a higher rate of no residual tumor.

4.2.1.2. MRI response

All patients in our study had locally advanced rectal cancer, defined by T3–T4 disease before treatment. After TNT, this proportion decreased to 78.8%, with statistical

significance ($p<0.001$). This means that 21.2% of patients achieved downstaging to T0–T2 on preoperative MRI. Our statistically significant findings suggest that the use of FOLFIRINOX in TNT not only reduces local invasion but may also help increase pCR rates and improve long-term prognosis. In addition, the conversion from T3–T4 to T0–T2 on MRI provides important information for surgeons regarding the feasibility of successful sphincter preservation, which was confirmed by the high sphincter preservation rate in our study. These data support the view that FOLFIRINOX is among the most effective regimens for local control in rectal cancer.

Before TNT, 69.4% of our patients had extensive nodal metastasis (N2), reflecting the advanced nature of mid–low rectal cancer at diagnosis. This is a poor-prognosis group with a high risk of local recurrence and distant metastasis and is considered one of the “high-risk” features in RAPIDO, including T4, N2, CRM positivity, and EMVI positivity. After TNT with FOLFIRINOX combined with chemoradiotherapy, the proportion of patients remaining N2 decreased sharply to 23.5%, with high statistical significance ($p<0.001$). TNT trials such as PRODIGE-23 and RAPIDO have also shown that intensified TNT increases nodal downstaging compared with standard preoperative chemoradiotherapy. This demonstrates the clear efficacy of FOLFIRINOX in controlling nodal disease, which is a key determinant of surgical feasibility and long-term prognosis.

4.2.1.3. Pathological response after surgery

In our study, postoperative pathology showed that 28.2% of patients achieved complete response (TRG 1). The proportions of patients with TRG 2 and TRG 3 were 27.1% and 25.9%, respectively, whereas TRG 4 and TRG 5 were less frequent, at 15.3% and 3.5%, respectively. Overall, 81.2% of patients showed evidence of tumor regression (TRG 1–3) after TNT with induction FOLFIRINOX and concurrent chemoradiotherapy, and 55.3% achieved good response, defined as complete response or only minimal residual tumor cells after treatment. Our TRG 1 (pCR) rate was fairly consistent with rates reported in TNT trials nationally and internationally. In Vietnam, preliminary results of total neoadjuvant treatment before surgery in stage II–III rectal cancer reported TRG 1, TRG 2, TRG 3, TRG 4, and TRG 5 rates of 31.4%, 37.2%, 20%, 11.4%, and 0%, respectively. The PRODIGE-23 trial, using induction FOLFIRINOX, reported a pCR rate of 28%, significantly higher than the 12% observed in the standard chemoradiotherapy group. Similarly, in RAPIDO, the pathological complete response rate was about 28% in the TNT group, showing that total neoadjuvant treatment substantially increases response compared with chemoradiotherapy alone.

Table 4.1. pCR rates in preoperative neoadjuvant treatment for rectal cancer

Study	Year	Regimen	No. of patients	pCR (%)
Nguyen Van Hieu	2018	CRT	31	6.5
Vo Quoc Hung	2022	CRT	85	3.5
		CRT	398	14.3
RAPIDO	2021	TNT (SCRT + FOLFOX/CAPOX)	423	28.4
		CRT	215	12.1
PRODIGE-23	2021	TNT (FOLFIRINOX + CRT)	212	27.8
		TNT (CRT + FOLFOX/CAPOX)	35	31.4
Nguyen Thi Ha	2023	TNT (CRT + FOLFOX/CAPOX)	35	31.4
		TNT (CRT + FOLFOX/CAPOX)	75	33.3
Nguyen Hai Hoang	2024	TNT (CRT + FOLFOX/CAPOX)	75	33.3
Our study	2025	TNT (FOLFIRINOX + CRT)	85	28.2

In addition to tumor regression, our study also recorded that 90.6% of patients who underwent total neoadjuvant treatment (TNT) before surgery experienced nodal downstaging after surgery compared with pretreatment status. Nodal downstaging not only increases the likelihood of curative resection but also has long-term prognostic significance, because post-treatment nodal stage (ypN) is considered one of the predictors of recurrence and survival. An analysis by Wan et al. in 2025 showed that patients who achieved ypN0 had a very high 5-year survival rate of up to 89%, comparable to that of patients who were cN0 at baseline, and superior to that of patients with persistent nodal positivity (ypN+) ($p = 0.0034$). Multivariable analysis in that study also identified ypN as an independent prognostic factor for overall survival. In Vietnam, early reports on TNT have likewise documented marked nodal downstaging. In a study from Military Central Hospital 108 including 35 patients, 94.3% showed nodal downstaging after TNT. The consistency between our findings and both domestic and international data further confirms the role of preoperative neoadjuvant treatment as an effective strategy for downstaging both the primary tumor and regional lymph nodes before surgery.

While TRG, pT, and pN individually assess the response of the primary tumor or lymph nodes after treatment, the NAR score is a composite scale (based on cT, ypT, and ypN) used as a tool for the early prognostic evaluation of total neoadjuvant treatment (TNT). This score has been shown to have strong prognostic value for recurrence risk and long-term survival in patients with rectal cancer treated with neoadjuvant therapy. According to international studies, a low NAR score reflects a good treatment response, whereas a high NAR score suggests a worse prognosis and a higher risk of recurrence. The prognostic value of NAR has been confirmed in several large studies, notably an analysis of 12,452 rectal cancer patients from the National Cancer Database conducted by Samer and colleagues. This study showed that NAR could clearly stratify risk: the low-NAR group (≤ 8) had a 5-year overall survival rate of 89.5%, compared with only 67.2% in the high-NAR group (≥ 16), a statistically significant difference ($p < 0.001$). Another study by Yanwu Sun, which analyzed 522 patients, reported a similar trend: the low-NAR group had a 5-year disease-free survival (DFS) of up to 85.6%, significantly higher than 47.2% in the high-NAR group ($p < 0.001$). The author concluded that NAR not only predicts recurrence and survival, but also allows earlier prognostication than waiting for long-term OS assessment, and therefore has been proposed as a surrogate endpoint in modern neoadjuvant studies. The use of NAR in our study is appropriate and has practical value. NAR not only reflects the overall effect of TNT on the primary tumor and lymph nodes, but also helps stratify prognosis early, supports decisions on postoperative adjuvant treatment, and optimizes long-term follow-up. With a low NAR rate in more than 40% of patients, this suggests that the TNT regimen we applied was clearly effective; at the same time, the high-NAR group could also be identified for closer follow-up or more intensive adjuvant treatment.

4.2.1.4. Factors associated with pathological response

In our study, factors such as age, sex, and pretreatment T and N stage showed no statistically significant differences between patients who achieved pathological complete response and those who did not ($p > 0.05$). Similarly, pretreatment clinicoradiologic factors, including the distance from the tumor to the anal verge, MRF status, and EMVI status on pretreatment MRI, were not significantly associated with pCR. For poorly differentiated/mucinous histology, univariable analysis showed a significant association with pathological complete response. However, the number of such cases in our study was small, and after multivariable logistic regression this factor was no longer statistically significant; therefore, there is insufficient evidence to conclude that it is an independent

predictive factor. In contrast, endoscopic response assessment after TNT showed clear prognostic value: patients in whom no tumor was detected, or only a scar/small fibrotic ulcer remained, had a markedly higher pCR rate than those with persistent visible tumor ($p < 0.001$). This finding is consistent with many clinical reports, in which meticulous endoscopic assessment combined with additional biopsy when necessary may suggest patients who are likely to achieve pCR or near-pCR. However, compared with international reports, our findings, like most studies, also reflect a complex and inconsistent reality: almost no pretreatment factor has been universally accepted as a standard predictor of pCR. A large meta-analysis of neoadjuvant treatment for rectal cancer found that although many indicators have been studied, such as tumor size, distance from the anal verge, EMVI, MRF, and CEA, the ability to predict pCR remains very limited because of heterogeneity across studies.

4.2.2. Survival outcomes

4.2.2.1. Disease-free survival

Disease-free survival (DFS) is an important endpoint in evaluating treatment efficacy in rectal cancer, particularly in the context of total neoadjuvant treatment (TNT). In this study, we evaluated DFS in patients with locally advanced mid–low rectal cancer treated with induction FOLFIRINOX followed by preoperative chemoradiotherapy with capecitabine, in order to identify factors associated with prognosis and compare the results with the available literature. By definition, DFS was calculated from the initiation of treatment to the occurrence of recurrence or death from any cause.

In our study, after 5 years of follow-up, a total of 7 patients experienced recurrence, and the estimated 3-year DFS was 91.1%, while the 5-year DFS was 87.3%, which are highly favorable outcomes, comparable to those reported in major trials such as RAPIDO (77%), PROSPECT (81%), and PRODIGE-23 (75.7%). Table 4.2 summarizes DFS results from domestic and international studies. FOLFIRINOX is an intensive chemotherapy regimen combining 5-fluorouracil, oxaliplatin, and irinotecan, originally used in metastatic colorectal cancer. The rationale for moving this regimen into the neoadjuvant setting is to enhance tumor cell kill at the primary site and in regional lymph nodes, improve T and N downstaging, optimize the chance of sphincter-preserving surgery, reduce the risk of recurrence, and improve long-term survival outcomes. In the PRODIGE-23 trial, the TNT arm using induction FOLFIRINOX showed a significantly improved 3-year DFS compared with the CRT arm (HR = 0.69; 95% CI 0.49–0.97; $p = 0.034$). A systematic review and meta-analysis of 15 trials involving 3,579 patients showed that TNT significantly improved DFS (HR = 0.80; 95% CI 0.69–0.92; $p = 0.001$) compared with standard CRT. Accordingly, the use of total neoadjuvant treatment has increased in recent years. In the United States, TNT accounted for only 6.1% of cases in 2016, whereas conventional treatment represented 93.9%. However, after only 4 years, the proportion treated with the new regimen had risen to 34.6%. Among these, induction chemotherapy combined with long-course concurrent chemoradiotherapy was the most favored approach, accounting for nearly 70% of TNT cases.

Induction chemotherapy refers to chemotherapy administered first, before chemoradiotherapy, whereas consolidation chemotherapy is given after radiotherapy to add to the effect of radiation. Both approaches have their own advantages and disadvantages. Induction chemotherapy administered at the outset allows systemic treatment to begin as early as possible, when the tumor vasculature and microenvironment are still relatively intact. One advantage of induction chemotherapy is the ability to individualize treatment based on the initial tumor response to chemotherapy, thereby helping predict and potentially modify the subsequent treatment strategy. In contrast, consolidation chemotherapy is given with the aim of prolonging the interval between completion of radiotherapy and surgery in order to increase the response rate; in addition, consolidation

chemotherapy itself contributes to the eradication of the local tumor and any micrometastatic disease. The choice between these two strategies remains controversial. Comparative studies between induction and consolidation chemotherapy have been conducted; however, to date there is no evidence demonstrating a clear superiority of either approach.

Table 4.2. Disease-free survival in published studies

Study	Year	Regimen	DFS (%)	Follow-up duration
Nguyen Van Hieu	2018	CRT	78.1	3 year
PRODIGE-23	2021	CRT	68.5	3 year
		CRT	62.5	7 year
		TNT (FOLFIRINOX + CRT)	75.7	3 year
		CRT	67.6	7 year
STELLAR	2022	CRT	62.3	3 year
		TNT (SCRT + CAPOX)	64.5	3 year
OPRA	2020	TNT (Induction)	76	3 year
		TNT (Consolidation)	76	3 year
CAO/ARO/AIO-12	2019	TNT (Induction)	73	3 year
		TNT (Consolidation)	73	3 year
Our study	2025	TNT (FOLFIRINOX + CRT)	91.1	3 year
		CRT)	87.3	5 year

Our study had a relatively small sample size and a low number of recurrence events (7 patients), which may have contributed to an overall DFS rate higher than what might be observed in larger multicenter trials. Therefore, although the figures of 91.1% and 87.3% are very encouraging, they should be interpreted cautiously, and longer follow-up together with a larger sample size will be necessary to confirm the durability of this DFS rate.

4.2.2.2. Factors associated with disease-free survival

When analyzed according to pathological response, DFS tended to be higher in the TRG 1–2 group than in the TRG >2 group, but the difference was not statistically significant ($p = 0.25$). This may be due to the low number of events, with only 7 recurrences, and also because TRG mainly reflects local response and does not fully capture the risk of micrometastatic disease. Similarly, the pCR group also showed a tendency toward longer DFS than the non-pCR group, but the difference was not statistically significant. This phenomenon may occur in studies with a small sample size or a low recurrence rate. Although pCR has traditionally been considered a favorable prognostic factor for survival, data from meta-analyses suggest that it is not an absolute prognostic determinant. A recent meta-analysis of 25 randomized controlled trials involving 11,882 patients did not show a statistically significant association between pCR and DFS/OS. In the pooled analysis by Maas et al., although pCR was associated with better 5-year DFS/OS, a non-negligible proportion of patients with pCR still developed distant metastases, indicating that pCR does not completely eliminate metastatic risk. Therefore, while pCR, or a low TRG, is important and valuable in assessing early treatment response, predicting long-term prognosis based solely on pCR is insufficient; pCR should be considered as one component of a multivariable prognostic model.

One notable finding in our study was the role of the NAR score. Although previous studies have identified 8 as the cutoff for the low-risk group, our study showed that patients with NAR <8 tended to maintain very high DFS throughout follow-up, whereas those with NAR ≥ 8 experienced more events, although the difference was not statistically significant ($p > 0.05$). On the other hand, using the intermediate cutoff of 12, the NAR <12

group showed significantly better DFS than the NAR ≥ 12 group ($p = 0.017$). This finding suggests that NAR has prognostic value in the TNT setting, reflecting the overall effect of treatment on both the primary tumor and the lymph nodes. This result is consistent with international studies; for example, in the CAO/ARO/AIO-04 trial, the 3-year DFS rates were 91.7% in the low-NAR group, 81.8% in the intermediate-NAR group, and only 58.1% in the high-NAR group. The strength of NAR compared with TRG or pCR alone is that it combines cT, ypT, and ypN, thereby simultaneously reflecting both local response and nodal metastatic burden. This allows more accurate classification of patients according to recurrence risk. As observed in our study, although the low-TRG or pCR groups did not show statistically significant DFS differences, the NAR score still showed a prognostic signal, especially at the cutoff of 12; however, this finding should be interpreted with caution because of the small number of events.

Overall, the survival outcomes in our study suggest that TNT with induction FOLFIRINOX combined with preoperative concurrent chemoradiotherapy provides a high disease-free survival rate, even in patients with advanced T3–T4 disease. Although TRG or pCR did not show statistically significant differences because of the low number of events, NAR still stands out as a potential prognostic marker that may help guide follow-up and postoperative adjuvant treatment. However, long-term DFS/OS follow-up and multivariable analyses are still needed to identify independent prognostic factors in this study population.

4.3. ADVERSE EFFECTS OF THE REGIMEN

4.3.1. Adverse effects during induction chemotherapy

FOLFIRINOX, consisting of oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil, is an intensive multidrug chemotherapy regimen commonly associated with toxicities, mainly hematologic toxicities such as leukopenia, neutropenia, and thrombocytopenia, as well as nonhematologic toxicities such as nausea, vomiting, diarrhea, and peripheral neuropathy. Most events are mild to moderate (grade I–II), but more severe events (grade III–IV) may occur in some patients, especially neutropenia, requiring close monitoring and timely intervention.

In our study, the hematologic and nonhematologic toxicities of induction chemotherapy were generally mild to moderate, indicating good treatment tolerability in patients with locally advanced rectal cancer. Most adverse effects by cycle were grade I–II; grade III–IV neutropenia occurred in only 4.0% of cycles, and grade III–IV total leukopenia occurred in 1.0%. Grade II–IV thrombocytopenia and hemoglobin reduction were both very low, at $<2\%$. When analyzed by patient, toxicities were also mainly grade I–II. Grade $\geq$ III toxicities included 2.4% leukopenia, 11.7% neutropenia, 1.2% thrombocytopenia, and 2.4% anemia. These rates are lower than those reported in many large studies using irinotecan- or oxaliplatin-containing regimens in the neoadjuvant setting.

In our study, hepatic and renal toxicities of induction FOLFIRINOX were mainly mild. Only 2 patients developed grade III AST elevation, and no grade III or higher renal toxicity was observed. Large reports have also shown that liver toxicity from oxaliplatin- and irinotecan-containing regimens usually manifests as mild transaminase elevation or sinusoidal liver injury and only rarely progresses to severe hepatic failure. Renal toxicity from oxaliplatin is considered much lower than that of other platinum compounds, although it may still occur in special circumstances such as underlying renal disease or concomitant use of other nephrotoxic agents.

Gastrointestinal adverse effects in our study were mainly mild, and only 2 cases of nausea/vomiting $\geq$ grade III were recorded. This toxicity profile is consistent with

international reports, in which pooled analyses of FOLFIRINOX show that most gastrointestinal events are grade I–II, whereas severe toxicity (grade $\geq$ III) remains relatively low because of dose adjustment and supportive care. Similarly, the PRODIGE-23 trial showed that diarrhea and nausea were common adverse effects of FOLFIRINOX, but severe events were not predominant and could be managed with antiemetic prophylaxis and appropriate dose modification. The main mechanisms of gastrointestinal toxicity are related to irinotecan (causing diarrhea and nausea) and 5-FU (causing stomatitis and diarrhea). Overall, our findings are consistent with the international literature, showing that although FOLFIRINOX is an intensive regimen, it can be well tolerated in the neoadjuvant setting if gastrointestinal toxicities are closely prevented and monitored.

Neurologic toxicity in our study was mainly mild, with grade I peripheral neuropathy accounting for 5.2%, and no grade $\geq$ III events were observed. One important factor contributing to this low rate is that our regimen used oxaliplatin for only 6 induction cycles, thereby limiting cumulative dose, which is the main mechanism of neurotoxicity. This rate is considerably lower than those reported in international studies, where pooled analyses have shown neuropathy rates ranging from 4% to 98% depending on dose and number of cycles. Thus, the low neurologic toxicity in our study may reflect the effectiveness of limiting the cumulative oxaliplatin dose and number of cycles, thereby reducing the risk of significant neurotoxicity compared with standard international regimens.

Taken together, the toxicity profile of TNT in our study was favorable, with lower severe toxicity rates than in most major international studies. This is clinically important because lower toxicity helps patients complete the regimen, reduces treatment interruptions, limits dose reductions, and increases the likelihood of achieving pathological response. In addition, maintaining quality of life throughout neoadjuvant treatment helps patients proceed to chemoradiotherapy and surgery on schedule.

Table 4.3. FOLFIRINOX toxicity across studies

Grade 3/4 adverse event with FOLFIRINOX	PRODIGE–23 (%)	Our study (%)
Leukopenia	2.6	2.4
Neutropenia	16.9	11.7
Thrombopenia	1.3	1.2
Anemia	0.9	2.4
Elevated liver enzymes	2.2	2.4
Diarrhea	11.1	4.7
Nausea	6.2	4.7
Vomiting	4.9	4.7
Peripheral neuropathy	2.2	0.0

4.3.2. Adverse effects during concurrent chemoradiotherapy

In our study, gastrointestinal events after concurrent chemoradiotherapy with capecitabine before surgery were mainly mild to moderate: grade I proctitis accounted for 21.2%, grade II for 10.6%, and grade III for 4.7%. Genitourinary toxicity was uncommon: grade I cystitis occurred in 5.8% of patients, and there was only 1 case of vaginitis (1.2%), with no severe events such as bladder failure, urinary obstruction, or severe ulceration. Skin toxicity after preoperative chemoradiotherapy was also mainly mild, with grade I dermatitis in 16.5% and grade II in 4.7%; no severe grade $\geq$ III events were observed.

Previous studies have also shown that preoperative chemoradiotherapy for rectal cancer is generally well tolerated. The CAO/ARO/AIO-12 trial reported grade I–II dermatitis in 31% and grade III dermatitis in 3%; grade I–II proctitis in 42% and grade III proctitis in 3%; grade I–II cystitis in 19% and grade III cystitis in 1%; adverse effects also included grade I peripheral neuropathy in 18% of patients, grade I–II nausea in 36%, grade I–II vomiting in 10%, and grade I–II diarrhea in 56%. Hoàng Văn An et al. (2022), in 73 patients with stage III rectal cancer treated with preoperative concurrent chemoradiotherapy, reported grade I–II dermatitis in 30%, grade I–II proctitis in 27.3%, grade III proctitis in 1.3%, and cystitis in 8.2%. Nguyễn Thị Ngọc (2023), in 49 patients with stage II–III rectal cancer treated with concurrent chemoradiotherapy, reported mild hand-foot syndrome in 10.9%, nausea in 8.7%, grade I vomiting in 10.2%, and grade I–II diarrhea in 17.4%, with no grade III–IV toxicity. In the study by Nguyễn Hải Hoàng et al. (2024), involving 73 patients treated with TNT using preoperative chemoradiotherapy and consolidation chemotherapy, grade I dermatitis occurred in 34.2% and grade II in 6.8%; grade I proctitis occurred in 12.3% and grade II in 5.5%; no grade III or IV events were observed. Overall, preoperative chemoradiotherapy for rectal cancer is well tolerated, with no severe complications reported in many domestic and international studies.

4.4. STRENGTHS AND LIMITATIONS OF THE STUDY

This study was conducted at three experienced oncology centers, with relatively standardized procedures for patient selection, treatment, and response assessment. Patients were followed throughout the entire treatment course, and a broad range of clinically relevant outcomes was evaluated, including endoscopic and magnetic resonance imaging responses, pathological complete response, tumor downstaging, the feasibility of curative and sphincter-preserving surgery, disease-free survival, and treatment-related toxicities during both induction chemotherapy and concurrent chemoradiotherapy.

Our study still has several limitations. First, the sample size of 85 patients remains relatively small, which may affect the precision of estimates and limit the value of subgroup analyses. In addition, although the study was conducted at three hospitals, convenience sampling of patients who met treatment and follow-up requirements may have introduced selection bias, thereby affecting the representativeness of the study population. Moreover, this was a descriptive longitudinal study without a control group, so it does not allow direct comparison of the efficacy and toxicity of this regimen with other treatment strategies, nor does it provide sufficient basis to establish causal relationships between the intervention and treatment outcomes. Therefore, further studies with larger sample sizes, more rigorous designs, and appropriate control groups are needed to more fully evaluate the value of this regimen.

CONCLUSION

The study of 85 patients with locally advanced mid–low rectal cancer treated with induction FOLFIRINOX and preoperative radiotherapy combined with capecitabine at Hanoi Medical University Hospital, Military Hospital 103, and K Hospital from January 2019 to December 2025 showed that:

1. Treatment outcomes of induction FOLFIRINOX and concurrent chemoradiotherapy with capecitabine before surgery in patients with locally advanced mid–low rectal

Post-total neoadjuvant therapy, preoperative MRI showed significant reductions in the proportions of patients with T3–4 tumors and N2 nodal disease compared with pretreatment assessments ($p < 0.001$). The endoscopic complete response rate was 21.2%.

All patients who underwent surgery achieved an R0 resection. Among them, 73 patients (85.9%) underwent curative sphincter-preserving surgery. The pathological complete response rate was 28.2%, and postoperative histopathological examination demonstrated nodal downstaging in 90.6% of patients compared with pretreatment staging.

Endoscopic response was significantly associated with pathological complete response. Most patients with no residual tumor detected on endoscopy achieved pCR, with a statistically significant difference ($p < 0.001$).

The 3-year and 5-year disease-free survival rates were 91.1% and 87.3%, respectively. An NAR score of <12 was identified as a favorable prognostic factor for disease-free survival.

2. Adverse effects of the regimen

Adverse effects of induction chemotherapy were mainly grade I–II. Grade $\geq$ III toxicities included leukopenia in 2.4%, neutropenia in 11.7%, thrombocytopenia in 1.2%, and anemia in 2.4%. Two patients developed grade III AST elevation, and 4 patients had nausea/vomiting $\geq$ grade III.

Adverse effects during concurrent chemoradiotherapy were mainly mild: grade I proctitis occurred in 21.2%, grade II in 10.6%, and grade III in 4.7%. Grade I cystitis was observed in 5.8% of patients, and only 1 case of vaginitis (1.2%) was recorded. Grade I dermatitis occurred in 16.5%, grade II in 4.7%, and no severe grade $\geq$ III event was recorded.

The completion rate of induction chemotherapy was 91.8%. Among these patients, the treatment delay rate was 25.9%, and the dose reduction rate during induction chemotherapy was 9.4%. The completion rate of concurrent chemoradiotherapy was 100%.

RECOMMENDATION

Our study showed that induction FOLFIRINOX chemotherapy combined with preoperative radiotherapy using capecitabine is a feasible treatment approach in patients with locally advanced mid–low rectal cancer. The initial results showed that the regimen was effective in downstaging tumors, increasing the pathological complete response rate, improving the likelihood of sphincter preservation, and improving disease-free survival.

Further studies with larger sample sizes, longer follow-up, and more detailed patient stratification are needed to more accurately assess the value of this regimen with regard to survival outcomes and treatment safety. In addition, more in-depth investigation of the relationship between degree of response and individualized treatment strategies would be meaningful in clinical practice.