Neoadjuvant Strategies: Locally Advanced Rectal Cancer

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Clin Colon Rectal Surg 2017;30:383–386.

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Abstract

Keywords

- colorectal cancer
- rectal cancer
- neoadjuvant chemoradiation
- adjuvant chemotherapy
- survival

Colorectal cancer is one of the major leading causes of death in both men and women. The successful management of colon or rectal cancer demands a multidisciplinary approach. In the last few years, significant improvement has been noticed in the management of localized rectal cancer to reduce local recurrence and obtain complete pathological response following appropriate surgical steps, if necessary. Implementation of neoadjuvant therapy not only enhances disease control, it may also ensure sphincter preserving procedures or organ-preserving options. This article principally concentrates on the current neoadjuvant treatment for locally advanced rectal cancer and the prognostic outcomes of such therapy, including a discussion on the historical perspective.

Overview of Colorectal Cancer Treatment

According to the American Cancer Society, the number of colorectal cancer patients for 2016 in the United States is estimated to reach 134,490.¹ The outcomes of colorectal cancer depend on the stage of the disease. In general, surgery is the definitive option (► **Table 1**) for nonmetastatic rectal cancer. The upper and middle rectal lesions can be generally managed with low anterior resection (LAR) with the preservation of anal sphincter. Management of lower rectal lesions (within 5 cm of the anal verge) is more challenging. Abdominoperineal resection (APR) has been the most frequently performed procedure in an attempt to provide optimal local control for such cases. However, this procedure inevitably leads to a permanent colostomy and significantly impacts the quality of life with functional consequences.

Evaluation before Considering Neoadjuvant Therapy for Rectal Cancer

Besides pathologic review, rectal patients should undergo clinical staging to be considered for neoadjuvant treatment. The following tests should be considered:

- Carcinoembryonic antigen (CEA)
- Proctoscopy and digital rectal examination (DRE)

- High-resolution pelvic magnetic resonance imaging (MRI)
- Endorectal ultrasound (if MRI is not possible)
- Computerized tomography (CT) of chest
- CT or MRI of abdomen with contrast

Risk Stratification

Based on the MRI-evident extramural spread, nodal status, circumferential resection margin, position of tumor, and extramural venous invasion, rectal cancer can be subdivided into low-risk, moderate-risk, and high-risk variants. Data suggest that mesorectal invasion of > 5 mm, circumferential margin positivity, N2, extramural venous invasion, and sacral side involvement are associated with high risk of recurrence.^{2,3}

In summary, according to the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study,⁴ the group of rectal patients with good prognosis are characterized by:

- MRI-negative circumferential margin
- Negative extramural invasion
- T2/T3a/T3b
- <5 mm spread from the muscularis propria
- Negative involvement of the intersphincteric plane, regardless of MRI nodal status

Issue Theme New Horizons in Rectal Cancer Management; Guest Editor: Rodrigo Oliva Perez, MD, PhD

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Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0037-1606372>.
ISSN 1531-0043.

Table 1 Outline of treatment for colon and rectal cancer by stage

Stage	Colon	Rectum
I	Surgery	Surgery
II	Surgery	Neoadjuvant chemoradiation therapy followed by surgery ± adjuvant chemotherapy
III	Surgery ± adjuvant chemotherapy	Neoadjuvant chemoradiation therapy followed by surgery ± adjuvant chemotherapy
IV	Surgery, neoadjuvant chemotherapy followed by surgery, palliative chemotherapy, palliative radiation therapy, targeted therapy ± chemotherapy	Surgery, neoadjuvant chemotherapy followed by surgery, palliative chemotherapy, palliative radiation therapy, targeted therapy ± chemotherapy

Indication(s) for Neoadjuvant Therapy

Even though for many years surgery has been the only definitive option for localized rectal cancer, high recurrence rates have directed the overall treatment decision. The intention to administer neoadjuvant chemoradiation is to minimize the risk for local recurrence. The neoadjuvant chemoradiation has become the standard for stage II (cT3–4, N0, M0) and stage III (cT1–4, N+, M0) rectal cancer before surgery. However, as previously suggested by data provided from the MERCURY studies, neoadjuvant therapies are now frequently restricted to high-risk patients using preoperative MR imaging.

Neoadjuvant Approaches

Although neoadjuvant combined chemoradiation is considered the standard approach before definitive surgical procedure for localized rectal cancer, other neoadjuvant modalities are also available.

Neoadjuvant Radiation (Short-Course Radiation Therapy) versus Surgery Alone

There is evidence that preoperative radiation therapy (RT) reduces the risk of local recurrence. According to a meta-analysis of 8,507 patients from 22 randomized trials analyzed by Gray et al, the most notable finding was the yearly lower recurrence rate (46.0% less) in the group who had preoperative RT compared with the group who had surgery alone

($p = 0.00001$).⁵ However, the analysis found that the overall survival was not statistically significant between the groups (mortality: 62.0% for patients with preoperative radiation treatment vs. 63.0% for patients with surgery only, $p = 0.06$).

The clinical benefit of administration of RT before radical surgery (total mesorectal excision [TME]) was also reported in a Dutch randomized rectal cancer trial.⁶ In this study, 1,861 locally advanced rectal patients were randomly assigned into two groups: 924 patients had received short-course RT (5 Gy) for 5 days (a total of 25 Gy) before TME, and 937 patients had upfront TME. Baseline features showed no statistical significance between the groups, and local recurrence rate at 2 years was more favorable for the RT group (2.4 vs. 8.2%, $p < 0.001$). The findings on local recurrence from the 12-year median follow-up showed sustained benefits in local disease control in the preoperative RT group.⁷ The study concluded that for patients being treated with preoperative radiotherapy, there was more than a 50% reduction of local recurrence rate. The outcomes in local disease control of clinical trials on short- or long- course preoperative radiotherapy are discussed in ►Table 2.^{7–10}

Short-Course Radiation Therapy versus Long-Course Chemoradiation

Besides the short-course preoperative RT (5 Gy each day for 5 days), a longer course of radiation of total 50.4 Gy (1.8 Gy in 28 fractions) for approximately 5 weeks in combination with chemotherapy is being practiced as a standardized care in

Table 2 Phase III trials on short- or long-course neoadjuvant radiation administration

Study	N	RT dose (Gy), total/fraction	Local recurrence (%)			Reference
			With RT	Without RT	p-Value	
Swedish rectal cancer study	1,168	25/5	9.0	26.0	<0.001	Folkesson et al ⁸
Dutch colorectal cancer group, TME study	1,861	25/5	5.0	11.0	<0.0001	van Gijn et al ⁷
			With RT	With CRT	p-Value	
TROG 0104, Australian Tans–Tasman Radiation Oncology Group	326	25/5 50.4/28	4.4	7.5	0.24	Ngan et al ⁹
Polish study	316	25/5 45/25	9.0	14.2	0.17	Bujko et al ¹⁰

many institutions. The rationale for the addition of a chemotherapeutic regimen is based on the theory that it will act as a radiosensitizer as well as may address the concurrent systemic disease. There are only two principal studies available that compare the outcomes of short-course RT versus long-course chemoradiation therapy (CRT).

The Trans-Tasman Radiation Oncology Group compared the local recurrence and 5-year overall survival rates of T3 rectal cancers undergoing these two preoperative regimens (► **Table 2**).⁹ Out of 326, equal numbers of patients (163 each) were assigned to the two arms. The study found no statistical difference for local recurrence, distant recurrence, relapse-free survival, overall survival, or late toxicity.

In another comparison study reported by Bujko et al, 312 patients were randomized either into a group who had received short course of preoperative radiation only or a group who had completed preoperative chemoradiation (► **Table 2**).¹⁰ This study also revealed no statistical significance between the groups in terms of survival, local control, or late toxicity.

Similarly, based on a meta-analysis of these two studies, nonsignificant differences were observed for local recurrence (hazard ratio [HR] = 0.86, confidence interval [CI] = 0.50–1.48, $p = 0.58$), and similarly overall survival (HR = 0.94, CI = 0.71–1.25, $p = 0.68$).¹¹

Even though no differences in local disease control or survival were observed, long-course CRT was consistently associated with improved primary tumor regression.

Neoadjuvant Chemoradiation

The most common CRT regimen is the combination of radiation therapy and 5-fluorouracil (5-FU)-based chemotherapy. It has been suggested that infusional 5-FU may offer a higher chance of a complete response than bolus 5-FU¹² with this approach.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 study was conducted to evaluate different

5-FU-based regimens in the neoadjuvant setting in combination with RT. A total of 1,608 patients clinically diagnosed with stage II or III receiving long-course RT (4,500 cGy in 25 fractions plus a boost of 540 cGy to 1,080 cGy in daily fractions for 3 to 6 days) were randomized into four groups, namely, continuous IV infusion 5-FU (225 mg/m² for 5 days per week) with or without IV oxaliplatin (50 mg/m² per week for 5 weeks) and oral capecitabine (825 mg/m² bid 5 days per week) with or without oxaliplatin (50 mg/m² per week for 5 weeks). The study results showed no statistical difference between capecitabine with preoperative RT and continuous infusion of 5-FU with preoperative RT in terms of pathological complete response (pCR), sphincter saving surgery (SSS), or surgical downstaging (SD) with corresponding p values of 0.12, 0.59, and 0.62, respectively. It was also demonstrated that the addition of oxaliplatin did not favorably alter these primary outcomes. Administration of oxaliplatin resulted in significantly more toxicity rates (grade 3/4 diarrhea, $p < 0.0001$). Ongoing trials on improving major outcomes (local control, survival, and/or organ preservations) are listed in ► **Table 3**.

Addition of Adjuvant Chemotherapy after Surgical Treatment

As a component of the multimodality approach, postoperative chemotherapy has been practiced for locally advanced rectal cancer. Historically, adjuvant 5-FU results in an improved overall survival (OS) for patients with stage II or III rectal cancer.^{13,14} According to Petersen et al, in a meta-analysis of a total of 21 RCTs, there was a significant mortality reduction (nearly 17%) in patients with adjuvant chemotherapy compared with those who underwent observation alone after radical surgery (HR = 0.83, CI: 0.76–0.91).

In addition, in parallel with colon cancer, it was expected that adjuvant chemotherapy would result in a 25.0 to 30.0% risk reduction for distant metastasis and death.¹⁵ Therefore, patients with stage II and III rectal cancer are recommended

Table 3 Tentative clinical trials for rectal cancer¹⁶

Study	Primary endpoints	Stage	Country
TREK	Local control	III	United Kingdom
GRECCAR 4	Local control	II	France
HEBBERT	Local control	II	Netherlands
RAPIDO	Survival improvement	III	Sweden
PRODIGE	Survival improvement	II/III	France
MSKCC	Survival improvement	III	United States
PROSPECT	Survival improvement	III	United States
KIR	Survival improvement	III	Canada
PRODIGE NACRE	Toxicity reduction	III	France
GRECCAR 12	Organ preservation	III	France
OPERA	Organ preservation	III	Europe
STAR-TREK	Organ preservation	II	United Kingdom and Netherlands

to receive 4 months of adjuvant 5-FU-based chemotherapy with or without oxaliplatin following preoperative chemoradiation and TME.

The final results of a multicenter randomized phase III trial (German CAO/ARO/AIO-04) showed that an addition of oxaliplatin to both 5-FU-based neoadjuvant chemoradiation and adjuvant chemotherapy improved disease-free survival in patients staged clinically as cT3–4 or cN1–2 rectal cancer (HR = 0.79, CI: 0.64–0.98, $p = 0.03$).¹⁶ The benefit of folinic acid (leucovorin)–fluorouracil (5-FU)–oxaliplatin (FOLFOX) as adjuvant therapy has been described in the adjuvant oxaliplatin in rectal cancer (ADORE) trial.¹⁷ The study revealed that adjuvant FOLFOX improved 3-year disease-free survival compared with 5-FU/leucovorin (LV, 71.6 vs. 62.9%, HR = 0.657, CI = 0.434–0.994, $p = 0.047$).

However, there are also some recent studies that do not show benefit of adjuvant therapy following radical surgery and neoadjuvant CRT (EORTC 22921, CHRONICLE, Italian, and PROCTOR/SCRIPT).^{18–20} These results may reflect the fact that the overall benefit of adjuvant therapy may be less than expected following neoadjuvant treatment for rectal cancer.

Conclusion

Preoperative neoadjuvant chemoradiation has improved the outcomes of locally advanced rectal cancer in terms of local control. Stratification of risk based on preoperative imaging may identify patients that benefit the most from preoperative treatment and should be central in the design of future trials. Chemotherapy regimens based on 5-FU used concurrently with RT may provide maximal primary tumor response even though there is no evidence for superior local disease control in randomized trials. Adjuvant treatment after neoadjuvant CRT and radical surgery with or without oxaliplatin have shown inconsistent survival benefits and are definitely of interest to future trials, particularly with the development of new agents.

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