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PERSONALIZED MEDICINE IN COLORECTAL CANCER (D CUNNINGHAM AND EC SMYTH, SECTION EDITORS)

Personalizing Therapy for Locally Advanced Rectal Cancer

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Abstract Locally advanced rectal cancer is usually treated with chemotherapy, radiation therapy, and total mesorectal excision. Although effective, this trimodality therapy is arduous and associated with treatment-related toxicity. It has become clear that some patients may not need to undergo all three modalities of treatment and can thus avoid some of the treatment-associated morbidity. Two such approaches include selective use of preoperative radiation and nonoperative management. Limiting radiation can reduce treatment related toxicity and eliminate radiation-induced toxicity, fibrosis, and bowel and urogenital dysfunction. As an alternative to radical surgery, nonoperative management offers the considerable advantage of organ preservation. Efforts are under way to identify genetic markers that could be used to predict treatment response and better individualize treatment.

Keywords Rectal cancer · Personalized therapy · Chemotherapy · Radiotherapy · Surgery · Total mesorectal excision · Organ preservation

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Introduction

The treatment of rectal cancer has evolved toward a strong focus on decreasing local-recurrence rates using a combination of modalities. Over the past 100 years, efforts to reduce local-recurrence rates have shifted from perfecting surgical technique to integrating surgery into a trimodality approach—chemotherapy, radiation, and surgery—which is now the standard of care for stage II and III rectal cancer [1]. Although the trimodality approach has helped improve outcomes, a subset of patients are overtreated at the cost of morbidity and functional deficits. Another concern is that while the trimodality approach has lowered local-recurrence rates, systemic recurrence rates have stayed the same.

Selection of the most appropriate treatment modality should be based on considerations such as functional and oncological outcomes and risk stratification. Multiple factors must be taken into account in determining the correct regimen and sequence, as well as the possibility of a nonoperative approach for individual patients. A patient's ability to complete trimodal therapy should be included among the factors considered. Despite reports of better tolerance and compliance with preoperative chemoradiation, trimodal therapy is arduous, and some patients are unable to complete all three modalities [2]. The appropriate sequence of treatment should be tailored with the goal of preventing local and systemic recurrence and optimizing functional outcomes. For patients with a complete clinical response to chemoradiotherapy (CRT), a watch-and-wait strategy should be considered.

In this chapter, we review the current evidence on personalizing rectal cancer treatment in terms of treatment sequencing, addition and elimination of treatment components, and organ preservation.

Historical Perspective

In the decades following the first R0 radical resection by W. Ernest Miles in 1908 [3], the rate of postsurgery local recurrence of rectal cancer was about 30%. With the widespread adoption of total mesorectal excision (TME), widely taught by Richard Heald in the 1980s and 1990s, the rates of local recurrence decreased to single digits [4].

Multiple randomized clinical trials have investigated the use of neoadjuvant and adjuvant therapy for rectal cancer. Postoperative chemotherapy was shown to lower recurrence rates from 25 to 16% in the 1985 National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial [5]. This finding set the stage for multimodality treatment of rectal cancer. The Swedish Rectal Cancer Trial was the first study to demonstrate that neoadjuvant radiotherapy helps prevent local recurrence and is the only study to show that neoadjuvant radiotherapy increases survival [6].

Dutch and German trials helped to further define the current standard of care by demonstrating that standardization of surgical technique in combination with preoperative chemotherapy reduced local-recurrence rates to 2.4% [2, 7]. In addition, the German study reported a twofold higher number of sphincter-preserving operations in the neoadjuvant chemotherapy group [2]. Based on these landmark studies, the current standard of care in the USA for stage II/III rectal cancer is trimodal therapy, which includes neoadjuvant radiation combined with radiosensitizing doses of chemotherapy, followed by TME in 6–12 weeks. This standardization of treatment for a heterogeneous population of patients with stage II/III rectal cancer has led to overtreatment of a subset of patients, necessitating a more personalized approach to rectal cancer treatment.

Neoadjuvant Chemotherapy

The current standard-of-care neoadjuvant chemotherapy for rectal cancer consists of oral administration of the fluorinated pyrimidine prodrug capecitabine (Xeloda; Roche), which has been shown to act as a radiosensitizer [8]. The NSABP R-04 trial recently studied the potential benefits of adding oxaliplatin to preoperative treatment. The findings of that trial showed that in patients with stage II/III rectal cancer who received neoadjuvant chemotherapy, the addition of oxaliplatin to standard therapy did not change local-recurrence rates, the likelihood of sphincter-preserving surgery, or the likelihood of surgical down-staging, while increasing treatment-related toxicity [9]. Therefore, oral capecitabine monotherapy combined with radiation remains the preferred treatment.

Addition of Systemic Chemotherapy

Despite the decrease in the rate of local recurrence of rectal cancer, the rate of distant relapse remains 30–40% [10]. As a result, there has been growing interest in the use of systemic chemotherapy in the neoadjuvant setting, aimed at treating both micrometastasis and the primary tumor. In a pilot study of 77 patients with locally advanced rectal cancer with poor-risk features, treated with neoadjuvant capecitabine-oxaliplatin followed by CRT and TME, Chau et al. [11] reported a 24% rate of pathological complete response, compared to an 8% rate in the German trial [2]. Symptomatic responses in the study by Chau et al. were seen at a median of 32 days in 86% of the patients. This treatment was validated for safety and feasibility in a Phase II clinical trial, which found a 20% rate of pathological complete response and minimal toxicity [12]. In a 2014 retrospective review, Cercek et al. [13•] reported a 29% rate of complete clinical response in patients who received FOLFOX (folinic acid, fluorouracil, oxaliplatin) induction therapy followed by CRT. That study also demonstrated a high rate of compliance. All patients were assessed every 8 weeks, and no tumor progression was seen in patients with stage II/III rectal cancer with poor-risk features.

Induction chemotherapy is attractive for multiple reasons. First, it allows for better compliance with the treatment plan. In a phase II study, Fernandez-Martos et al. [14] compared induction chemotherapy to adjuvant chemotherapy in patients with locally advanced rectal cancer. The group that received induction chemotherapy had significantly higher rates of completion of prescribed chemotherapy (91 versus 54%) and lower toxicity (19 versus 54%) than the group that received adjuvant chemotherapy. In addition, patients that receive induction chemotherapy and undergo restorative proctectomy with diverting ileostomy do not have to receive additional chemotherapy with a stoma in place. It allows for completion of chemotherapy without complications of an ileostomy. Induction therapy also allows for earlier closure of diverting ostomies, and as demonstrated by Chua et al. [12], it accelerates symptomatic relief. Induction chemotherapy can be utilized for bulky symptomatic tumors and tumors with systemic spread evidenced by positive locoregional lymph nodes.

Radiation Therapy

Neoadjuvant pelvic radiation therapies are categorized as either short course or long course. In general, short-course radiation therapy delivers 25 Gy (five fractions of 5 Gy each), followed by surgery 1 week later. This radiation therapy decreased local-recurrence rates in both the Swedish Rectal Cancer Trial and the Dutch trial [6, 7]. Short-term radiation therapy is associated with relatively low sphincter salvage rates and limited safety with concurrent chemotherapy.

Long-course radiation therapy (used in the German trial) delivers 50.4 Gy (28 fractions of 1.8 Gy each), followed by surgery 4–8 weeks later [2]. It produces toxic effects in up to 50% of patients [15, 16]. These effects can lead to poor compliance, with a reported 70% of patients unable to tolerate the entire course [17]. In addition, the functional impairments associated with radiation therapy can be debilitating, especially in young patients [17]. Radiation can cause fibrosis and autonomic nerve damage, which can lead to pelvic floor, fecal, and urinary dysfunction. The Dutch Colorectal Cancer Group reported incontinence in 68% of irradiated patients, compared to 38% in the nonirradiated group [18].

Proponents of long-course radiation therapy have cited higher rates of sphincter preservation and lower surgical morbidity compared with short-term radiation therapy. Proponents of short-course radiation therapy, on the other hand, emphasize lower costs and improved patient compliance. Multiple randomized controlled studies have compared the benefits of short-course and long-course radiation therapies. One of the trials, conducted by Bujko et al. [17], found that short-course radiation therapy did not differ from long-course radiation therapy in terms of patient survival, local control, or late toxicity.

The Trans-Tasman Radiation Oncology Group [19] compared long- and short-course radiation therapies in patients with T3N(any) disease who also completed 5 months of postoperative adjuvant chemotherapy. Again, the two types of radiation therapy did not differ in local or distant recurrence, overall survival, or radiation-associated toxicity. However, the 2% cumulative local-recurrence rate at 5 years for long-course radiation therapy was lower than the rate for short-course radiation therapy. Although this finding is clinically significant, it did not reach statistical significance because of the study's low power. In addition, for a subset of 79 patients with distal tumors, the authors reported a cumulative local-recurrence rate of 12.5% in patients who received short-course radiation therapy, compared to 0% in patients who received long-course radiation. A single-institution, phase II clinical trial of neoadjuvant short-course radiation followed by four cycles of modified FOLFOX-6 and then TME 4–5 weeks later reported a 28% pathological complete response rate and acceptable morbidity rates [20].

Patient Stratification

Despite the improvement in local-recurrence rates with radiation, many question the broad use of radiation therapy, given its negative impact on bowel and urogenital function. The current standard of administering radiation therapy to all patients with stage II/III rectal cancer leads to overtreatment of a subset of patients. Because this subset of patients is heterogeneous, a personalized treatment plan based on tumor biology and risk stratification is needed. The risk of recurrence was stratified by Gunderson and colleagues into the following risk groups: low (T1/2 N0), intermediate (T1/2 N1, T3N0), moderately high (T1/2 N2, T3N1, T4N0), and high (T3N2, T4N1/2). Based on data from large phase III rectal cancer trials, patients with intermediate-risk tumors have local recurrence rates of 6%, compared to 8–15% for the moderately high-risk group and 15–22% for the high-risk group. This translates into higher rates of 5-year overall survival for intermediate-risk patients (74–81%) compared to the moderately high-risk (61–69%) and high-risk (33–48%) groups [21].

Based on the above data, patients with locally advanced rectal cancer with poor-risk features clearly benefit from radiation. However, selective use of radiation in low- and intermediate-risk patients is reasonable in an attempt to avoid radiation-associated toxicity such as incontinence. This approach was examined in a prospective study of 32 patients with stage II/III rectal cancer who underwent neoadjuvant FOLFOX-based chemotherapy without radiation [22•]. All 30 patients who completed the neoadjuvant chemotherapy underwent an R0 resection. The rate of complete pathological response was 27% and 63% of patients showed tumor response rates of >80%. No pelvic recurrence was reported with a mean follow-up of 27 months. The rate of distant metastasis was 10% [22•]. These results need to be validated by larger randomized clinical trials.

The current international prospective randomized trial PROSPECT (Preoperative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME) N0148 is aimed at using radiation selectively rather than reflexively. The study enrolls patients with T3N0, T3N1, and T2N1 disease. The standard arm of the trial receives chemoradiation followed by TME, and the experimental arm receives FOLFOX for 6 weeks followed by restaging proctoscopy and MRI. Patients with greater than 20% response proceed directly to TME without preoperative radiation [23]. Those patients in the experimental arm that do not respond to induction FOLFOX receive preoperative chemoradiation. The proportion of patients that can avoid radiation, the rates of local and distant recurrence, functional outcomes, and correlative-science measures will be reported.

Timing of TME

The appropriate timing of surgery after completion of neoadjuvant treatment has also been a topic of investigation. Surgeons historically have been reluctant to delay surgery beyond 8 weeks after completion of neoadjuvant treatment. This is mainly due to concerns regarding micrometastasis during a period of waiting and increased risk of fibrosis from radiation that may lead to increased surgical morbidity. However, tumor response and tumor regression have been

shown to take months [24–26]. Multiple studies have demonstrated that tumor response is time dependent [27–30]. The Lyon R90-01 trial demonstrated that patients who underwent surgery at 6–8 weeks following neoadjuvant radiation (39 Gy over 17 days) had a higher pathological complete response rate than patients who underwent surgery at 2 weeks (26 and 10%, respectively), with similar oncological outcomes [25]. The 17-year follow-up showed no difference in survival between the two groups [31]. Kalady et al. [28] demonstrated that an interval >8 weeks resulted in a higher rate of pathological complete response than an interval of 6–8 weeks. They also found a consistent increase in the rate of pathological complete response in weeks 4–11. In a retrospective study of 189 patients, Kerr et al. [32] demonstrated that delaying surgery by >8 weeks after neoadjuvant CRT decreased postoperative morbidity [32]. However, a French multi-institutional phase III randomized trial (GRECCAR-6) found no significant difference in pathological complete response rates between patients who underwent surgery 7 weeks after CRT and patients who underwent surgery 11 weeks after CRT [33].

A recent European randomized controlled trial investigating the optimal timing of surgery after CRT in 237 patients found significant differences in both tumor downstaging and pathological clinical response rates for different intervals between CRT and surgery. In that prospective multicenter trial, the rate of pathological complete response was 20% in patients who underwent surgery 12 weeks after CRT and 9% in patients who underwent surgery 6 weeks after CRT. In addition, downstaging was more common in the 12-week-interval cohort (58%) than in the 6-week-interval cohort (43%) [34].

To address concerns regarding possible tumor progression during the interval between CRT and surgery, a phase II clinical trial studying the timing of rectal cancer response to CRT investigated the addition of chemotherapy following neoadjuvant chemoradiation. The study compared patients who received no additional chemotherapy to patients who received two, four, or six cycles of modified FOLFOX-6. The rate of pathological complete response was highest in patients who received six cycles of modified FOLFOX-6: 38%, compared to 18% in patients who received no additional chemotherapy [35•]. This increase in the rate of pathological complete response suggests that nonoperative management may be a viable treatment approach.

Nonoperative Management

In some patients, neoadjuvant CRT may lead to tumor downstaging or a complete pathological response. For such patients, the benefits of resection have been questioned. A pooled analysis of individual patient data demonstrated that patients with pathological complete response after CRT have higher survival rates than patients without such response (83.3 vs. 65.6%) [36]. Pathological complete response may be a surrogate indicator of a favorable biological tumor profile with a relatively low likelihood of local recurrence or distant metastasis.

Pathological complete response rates are variable and depend on many factors including initiation stage. A retrospective study of 361 patients with stage I–III rectal cancer reported a 27.4% rate of complete clinical response after 8 weeks of CRT [37•]. A watch-and-wait approach was adopted for those 99 patients. The disease recurred in 13 of the 99 watch-and-wait patients: five patients had local recurrence, seven patients had systemic recurrence, and one patient had both local and systemic recurrence. The mean interval between CRT completion and disease recurrence was 52 months. The 10-year rate of disease-free survival for patients with no recurrence was 90%, compared to 75.4% in patients who required salvage surgery for local tumor regrowth [37•].

In a prospective study of T2-4 N(any) rectal cancer, Habr-Gama et al. [38] examined survival in patients who had a complete clinical response after receiving an alternative CRT regimen. The patients received fluorouracil/leucovorin-based chemotherapy for three consecutive days every 21 days for six cycles, with three of the six cycles being concomitant with radiotherapy (5400 Gy total) [39]. The rate of initial complete clinical response was 68% ($n = 47$). Of the patients with a complete clinical response, 17% ($n = 8$) had a recurrence within the first 12 months of nonoperative management. An additional 10% of patients ($n = 4$) had local recurrence after more than 12 months of nonoperative management. The 3-year survival rates for patients with stage II disease and patients with stage III disease were 88 and 80%, respectively [38].

Despite the promising results, the organ preservation strategy of nonoperative management will remain outside of standard care for rectal cancer until sufficient evidence demonstrates that this strategy can achieve recurrence and survival rates that are equivalent or superior to those achieved with TME. Nevertheless, the organ preservation approach is increasingly becoming a viable option, at high-volume centers, particularly for frail patients and patients with a high risk of morbidity and death. For patients being considered for nonoperative management, a candid discussion of the risks, benefits, and experimental nature of the treatment plan is essential. Randomized clinical trials will need to identify predictors of recurrence and validate this treatment plan.

Biomarkers

Tumor response is dependent not only on radiation dose, chemotherapy regimens, and the timing of surgical intervention

but also on tumor biology [40]. Genetic biomarkers can be used to predict outcomes and select appropriate therapeutic modalities. An ideal biomarker would predict which patients will respond to CRT, thereby facilitating different treatment options for other patients.

Garcia-Aguilar et al. studied mutations and polymorphisms in 23 genes in 132 locally advanced tumors undergoing neoadjuvant treatment. The researchers discovered that the four most prevalent markers were *KRAS* mutation, *p53* mutation, *CCND1* G870A [AA] polymorphism, and *MHTFR* C677T [TT] polymorphism. Tumors with these genetic alterations did not achieve pathological complete response after CRT [41].

Mutations in epidermal growth factor receptor (EGFR) signaling pathways can predict efficacy of anti-EGFR therapies in colorectal cancer. Mutation of KRAS (which is a key component of this signaling pathway) is a strong predictor of lack of response to anti-EGFR monoclonal antibodies and could potentially serve as a response biomarker in rectal cancer patients treated with CRT. For a series of 39 patients treated with cetuximab and CRT, Bengala et al. reported higher response to CRT in patients with wild-type *KRAS* (37%) than in patients with mutated *KRAS* (11%) [42]. Garcia-Aguilar et al. reported similar results for 132 patients treated with fluorouracil-based CRT [41]. Chow et al. reported that in 229 CRT patients, *KRAS* mutation was independently associated with a lower rate of pathological complete response. That cohort of patients did not receive anti-EGFR treatment, but some patients received two, four, six, or eight additional cycles of FOLFOX [43]. In contrast to the above reports, however, some smaller studies found no correlation between *KRAS* mutation and response to treatment [44–46].

The role of the *p53* gene in cell cycle arrest, DNA repair, and apoptosis may affect acute cellular tumor responses to chemotherapy and radiation therapy. Multiple studies have examined the effects of *p53* on response to radiotherapy, and the results are mixed [41, 43, 47, 48]. However, the combination of *KRAS* and *p53* mutations has been reported to be negatively associated with pathological complete response in tumors treated with fluorouracil-based CRT [41, 43, 49]. Chow et al. reported an independent association of the combination of *KRAS* and *p53* mutations with lymph node metastasis [43]. These findings suggest that patients with both *KRAS* and *p53* mutations may not be appropriate candidates for the nonoperative approach.

Homozygosity for the A allele in CCND1, a regulator of the cell cycle, has also been reported to be associated with decreased response to CRT [41], although no such association was found in a series of 65 patients who underwent radiation therapy only [50]. Another genetic polymorphism, *MTHFR* C677T, associated with reduced activity of *MTHFR* (which plays an important role in DNA synthesis), may also decrease response to fluorouracil-based CRT [41, 51–53].

The feasibility of a biomarker assay in treatment of rectal cancer has been reported [49]. It is unlikely that a single biomarker can predict treatment response, but a combination of biomarkers may help identify patients who are most likely or least likely to benefit from a particular treatment. Most studies on potential biomarkers of rectal cancer response have been limited by the lack of uniformity in treatment paradigms and inadequate sample size [40].

Conclusion

The current standard of care for locally advanced rectal cancer, based on large randomized controlled studies, is a combination of neoadjuvant radiation and radiosensitizing chemotherapy followed by TME. This multimodality approach has been shown to decrease the rate of local recurrence. However, the rate of systemic recurrence continues to be high, which may indicate a need for the addition of induction chemotherapy in the neoadjuvant setting. This addition may also allow surgeons to increase the time interval between neoadjuvant CRT and surgery or eliminate the need for surgical intervention altogether. Given the poor functional outcomes of pelvic radiation, especially in combination with low anastomosis, radiation should be used selectively, depending on tumor characteristics and the likelihood of recurrence.

The evidence supporting selective use of trimodality therapy has come from retrospective and small prospective series. Larger, randomized trials have started accrual to answer some of these questions. However, it is unlikely that the nonoperative approach will be tested in a randomized fashion. Large prospective studies and registries with robust follow-up will be required to study this approach and identify patients that can avoid surgery.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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