Multidisciplinary Management of Locally Advanced Rectal Cancer: Neoadjuvant Approaches

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Abstract
Although tumor biology and genomics of colon and rectal cancer are no different, patients with locally advanced rectal cancer (LARC) require neoadjuvant fluoropyrimidine-based chemoradiation and total mesorectal excision. In addition to known clinical risk factors, improved algorithms integrating molecular tools are needed to stratify patients with LARC to improve treatment outcomes and reduce acute and long-term toxicities. Simply combining newer systemic or targeted agents with standard treatment in all patients yielded little success but added toxicities. This article reviews the historical data, current standards of care, and ongoing research efforts regarding biomarkers, molecular imaging, and personalized genomic information. (\textit{JNCCN} 2013;11:548–557)

Rectal cancer constitutes one-quarter of colorectal cancer cases and is the third most common gastrointestinal tract cancer, with approximately 40,000 cases diagnosed in the United States annually.\textsuperscript{1} Although the survival of patients with rectal cancer is comparable to that of similarly staged colon and sigmoid cancers,\textsuperscript{2} patients with locally advanced rectal cancer (LARC; T3–4 or node-positive LARC) experience a significantly higher local recurrence risk than their counterparts with colon cancer, requiring specific multimodality approaches.

This article reviews the biology, risk factors, and evolving treatment of LARC.

Important advances have been made in the past 3 decades in the multimodality treatment of patients with LARC. In the early 1970s, locoregional failure rates were as high as 45\%, with significant morbidity and mortality as a result of blunt surgical dissection of LARC.\textsuperscript{3,4} Total mesorectal excision (TME), the current surgical standard introduced in the 1980s, had reduced the local recurrence rate to 5\% to 8\% when combined with neoadjuvant chemoradiation and adjuvant chemotherapy.\textsuperscript{5,6}

Efforts to improve the current neoadjuvant standard of LARC through integrating newer chemotherapy or molecularly targeted agents to current fluoropyrimidine-based regimens have yielded limited results. Other important questions remain, including how to stratify best and poor responders, and how to tailor the current multimodality treatment based on tumor characteristics, interim response assessment, and predictive biomarkers to avoid unnecessary toxicity while optimizing local control, and reduce distal metastasis.

Biology of Rectal Cancers
Rectal cancer is defined based on the simple anatomic landmark of a primary tumor in the rectal canal below the peritoneal reflection. Thus, rectal cancer is molecularly similar to its colon cancer counterpart. Colorectal cancer is characterized by chromosomal instability and DNA repair defects, such as microsatellite instability (MSI), aberrant DNA methylation, and 2 dozen recurrent mutations involving oncogenes (K-ras, SOX9, ARID1A, FAM123B), tumor suppressor genes (APC, p53, SMAD4, PI3K), gene amplifications in ERBB2 and IGF2, and translocations in NAV-TCF7L1.\textsuperscript{7,8} The observation that the incidence of high MSI (MSI-H)
is extremely low in rectal cancer⁹ may explain the excellent response noted with chemoradiation in LARC.¹⁰ The presence of k-ras mutations in codon 13 may be associated with a lack of pathologic complete response (pCR).¹¹ HER2 expression was found in 27% of resected locally advanced rectal adenocarcinomas and may be associated with improved outcomes after multimodality therapy.¹² A key potential resistance mechanism in colorectal cancer may lie in the presence of cancer stem cells (CSCs), ranging from 2% to 5% in untreated tumors and up to 20% in treated tumors.¹³⁻¹⁵ The presence of CD133+ CSCs in the tumor tissues before and after radiation¹⁶,¹⁷ and in the peripheral blood¹⁸,¹⁹ predicts poor survival in rectal cancer and is associated with poor prognosis, likely because of variable clonal repopulations dynamics in the CSCs.²⁰ Male sex,²¹ the anatomy of the rectum, and positive pelvic nodes are among the most significant prognostic factors for LARC.²² Factors that increase the risk of local relapse include the extent of bowel wall penetration (T4), regional nodal involvement, and residual microscopic disease at the distal or circumferential resection margin (CRM) at the time of resection (Table 1). Recent meta-analyses suggest that anastomotic leak is another independent variable predicting poorer clinical outcomes and local recurrence.²³,²⁴

Although distant metastasis remains the most likely cause of death in patients with LARC, the strong effect of locoregional failure in predisposing to distant metastasis requires consideration in therapeutic decisions and evaluation of newer multimodality approaches. A positive CRM significantly predicts development of distant metastases with a hazard ratio (HR) of 2.8 (CI, 1.9–4.3), and although causality has not been established, the HR of death from any cause with a positive CRM was 1.7 (CI, 1.3–2.3).²⁵ Other studies have confirmed the impact of CRM on long-term outcomes in patients with resectable rectal cancer.²⁶

The Evolution of Current Treatment Strategies
Increased rates of local relapse despite radical curative resection prompted the evaluation of radiotherapy as a potential treatment modality. Multiple clinical trials, including a large meta-analysis, have shown that the use of preoperative or postoperative radiotherapy in patients with resectable rectal cancer decreases the risk of local relapse, with no definitive impact on overall survival,²⁷⁻²⁹ except for the Swedish Rectal Cancer trial, which showed improvements in local relapse rates and overall survival.³⁰,³¹ The use of combined modality therapy with radiation and chemotherapy in the adjuvant setting was adopted in the 1990s based on the results of 3 seminal studies, namely those of the Gastrointestinal Tumor Study Group (GITSG),³² the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01,³³ and the North Central Cancer Treatment Group (NCCTG).³⁴ All 3 trials suggested that adjuvant chemotherapy, radiation, or combined chemoradiation decreased the rates of local recurrence in patients with locally advanced rectal cancer (Table 2). As a result of the GITSG and NCCTG studies, postoperative adjuvant radiation and chemotherapy was set as a historical standard for locally advanced rectal cancer.

Introduction of TME had a significant impact on the local recurrence rate of LARC. The goal of this surgery is the en bloc resection of the rectal cancer with a complete pararectal lymph node dissection within the mesorectum. Meticulous sharp dissection and avoidance of disruption of the mesorectum are critical components of this technique. TME reduced the local recurrence rate to approximately 10%, equivalent to that achieved with conventional surgery with adjuvant chemoradiation.³⁵⁻³⁶ Overall, TME is associated with improvement in anatomic

<table>
<thead>
<tr>
<th>Table 1 Factors Affecting Local Recurrence After Surgery for Locally Advanced Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery-Related Factors</strong></td>
</tr>
<tr>
<td>Low anterior resection</td>
</tr>
<tr>
<td>Excision of the mesorectum</td>
</tr>
<tr>
<td>Extent of lymphadenopathy</td>
</tr>
<tr>
<td>Postoperative anastomotic leakage</td>
</tr>
<tr>
<td>Tumor perforation</td>
</tr>
<tr>
<td><strong>Tumor-Related Factors</strong></td>
</tr>
<tr>
<td>Anatomic location</td>
</tr>
<tr>
<td>Histologic type and grade</td>
</tr>
<tr>
<td>Pathologic stage</td>
</tr>
<tr>
<td>Circumferential radial margin</td>
</tr>
<tr>
<td>Invasion of neural, venous, or lymphatic systems</td>
</tr>
</tbody>
</table>

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resection, CRM clearance, and oncologic outcomes while reducing operative morbidity and preserving autonomic nerves in the pelvis. Although no randomized controlled trial demonstrates the superiority of TME over conventional dissection techniques, multiple studies now show that the local recurrence rates are significantly decreased with TME compared with historical controls (Table 3).35–37 In addition to optimal surgical techniques, the pathologic grading of the plane of surgery has been shown to be an important prognostic factor that defines local recurrence rates.38 A negative circumferential resected margin and a superior plane of surgery (mesorectal plane) were associated with low local recurrence rates (HR, 0.32; \(P=0.0011\)).

Reduced risk of local recurrence with TME initially raised the question of the ongoing need for perioperative radiation. Data from 5 different trials showed that the use of preoperative radiotherapy was beneficial in decreasing local recurrence rates (Table 4).28,31,39–41 Three meta-analyses also showed that preoperative radiotherapy improved local control, with 2 suggesting improved survival.42–44 These studies established the beneficial role of preoperative radiotherapy in the treatment of locally advanced rectal cancers in the era of TME.

The role of TME and preoperative radiotherapy has been well established in the treatment of LARC. Based on results of the adjuvant trials, the addition of chemotherapy to radiotherapy decreases local recurrence rates and improves overall survival (see Table 2). Multiple randomized clinical trials (Table 5) address the role of preoperative chemoradiation in improving local control and overall survival.45–48 Results from the seminal German Rectal Cancer Study established the preoperative chemoradiation approach as a standard of care for LARC.

### Chemotherapeutic Considerations in the Neoadjuvant Approach to Locally Advanced Rectal Cancer Treatment

The current standard of care in the United States for LARC is neoadjuvant chemoradiation with a fluoropyrimidine–based therapy, followed by TME in 5 to 10 weeks if possible, and subsequent adjuvant fluoropyrimidine-based chemotherapy for a total of 6 months.49 Neoadjuvant chemoradiation is better tolerated than postoperative chemoradiation and yields

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**Table 2 Selected Pre–Total Mesorectal Excision Adjuvant Trials for the Treatment of Locally Advanced Rectal Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Year</th>
<th>Treatment Arms</th>
<th>LR (%)</th>
<th>OS (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG(^{32})</td>
<td>227</td>
<td>1977–1988</td>
<td>Observation, RT, 40–48 Gy over 5.5 wk Chemotherapy, 5-FU + semustine Chemoradiation</td>
<td>55</td>
<td>44</td>
<td>Improved LR reduction with chemoradiation Underpowered to detect differences in OS</td>
</tr>
<tr>
<td>NCCTG(^{34})</td>
<td>240</td>
<td>1980–1986</td>
<td>RT, 45–50 Gy in 5 wk Chemoradiation, 5-FU + semustine</td>
<td>25</td>
<td>48</td>
<td>Improved LR reduction with chemoradiation</td>
</tr>
<tr>
<td>NSABP R-01(^{33})</td>
<td>555</td>
<td>1977–1986</td>
<td>Observation, RT, 46 Gy in 25 fractions Chemotherapy, 5-FU, semustine, vincristine</td>
<td>25</td>
<td>43</td>
<td>OS benefit from chemotherapy restricted to men</td>
</tr>
</tbody>
</table>

Abbreviations: LR, local recurrence; OS, overall survival; RT, radiotherapy.

**Table 3 Oncologic Outcomes With the Use of Total Mesorectal Excision in Patients With Rectal Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Local Recurrence (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacFarlane et al(^{36})</td>
<td>1993</td>
<td>135</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>Enker et al(^{35})</td>
<td>1995</td>
<td>246</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>Hainsworth et al(^{37})</td>
<td>1997</td>
<td>76</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Heald and Ryall(^{5})</td>
<td>1986</td>
<td>405</td>
<td>3</td>
<td>80</td>
</tr>
</tbody>
</table>
tumor downstaging, potentially improving sphincter preservation rate and quality of life.\textsuperscript{48} Notably, a nonstatistically significant trend toward improvement in sphincter preservation rates was noted in the NSABP R-03 trial, because the study was limited by low accrual.\textsuperscript{47}

**Infusional Versus Bolus 5-FU**

Studies have examined 5-FU either as a continuous infusion or in a bolus administration. An earlier study randomized 660 patients to receive either a continuous infusion of 5-FU (225 mg/m\textsuperscript{2}) or bolus 5-FU (500 mg/m\textsuperscript{2}) along with pelvic radiotherapy in an adjuvant setting. Results showed that protracted infusion of 5-FU improved local control rates and overall survival compared with bolus 5-FU, with differing toxicities.\textsuperscript{50} In contrast, the INT-0144 study reported comparable 3-year relapse-free and overall survival between bolus and continuous infusion 5-FU; however, longer follow-up is needed.

**Capecitabine**

Capecitabine, an oral fluoropyrimidine prodrug when used as a radiation sensitizer, showed similar pathologic complete response and increased rates of sphincter-sparing surgery compared with continuous-infusion 5-FU in multiple phase II and III studies.\textsuperscript{51–53,54} Hofheinz et al\textsuperscript{54} randomized 392 patients to receive either capecitabine or 5-FU–based chemoradiation and systemic therapy. Limitations in design include the mixture of neoadjuvant and adjuvant chemoradiation approaches in both arms. The study showed no change in local recurrence or 5-year overall survival rates despite an improved 3-year disease-free survival rate in the capecitabine arm (75% vs 66%). Capecitabine also resulted in increased rates of tumor downstaging (52% vs 39%) and node-negative disease (71% vs 56%) compared with 5-FU. In NSABP R-04, another phase III trial, capecitabine was compared with infusional 5-FU with or without the addition of oxaliplatin. Preliminary results showed no statistical difference in tumor downstaging, pCR, or sphincter preservation. Increased gastrointestinal toxicity was noted in the arms that received oxaliplatin.\textsuperscript{55} These 2 phase III trials suggest that oral capecitabine is a reasonable alternative to 5-FU for patients with LARC who require multimodality therapy.

**Oxaliplatin**

Of 4 randomized phase III trials that combined oxaliplatin with a fluoropyrimidine in the neoadjuvant approach to treat LARC, all except the German study showed increased toxicities with no benefits in pCR. To date, no benefits in survival or distant metastasis have been noted (Table 6).\textsuperscript{55–58} A fifth trial, PET-ACC-6, has completed accrual and results are pending (ClinicalTrials.gov identifier: NCT00766155). Hence, the use of oxaliplatin in the neoadjuvant

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Treatment Arms</th>
<th>LR (%)</th>
<th>5-Year OS (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch\textsuperscript{41}</td>
<td>1996–1999</td>
<td>1805</td>
<td>TME Preoperative RT (25 Gy for 5 wk) + TME</td>
<td>11</td>
<td>5</td>
<td>No difference Improved LR control</td>
</tr>
<tr>
<td>Swedish\textsuperscript{50}</td>
<td>1987–1990</td>
<td>908</td>
<td>Non-TME Preoperative RT (25 Gy for 5 wk) + non-TME</td>
<td>27</td>
<td>11</td>
<td>58 48 Use of preoperative RT improves survival</td>
</tr>
<tr>
<td>UK MRC\textsuperscript{29}</td>
<td>1981–1989</td>
<td>279</td>
<td>Non-TME Preoperative RT (40 Gy for 20 wk) + non-TME</td>
<td>46</td>
<td>36</td>
<td>24 31 Improved LR control but no change in OS</td>
</tr>
<tr>
<td>EORTC\textsuperscript{28}</td>
<td>1976–1981</td>
<td>466</td>
<td>Non-TME Preoperative RT (34 Gy for 15 wk) + non-TME</td>
<td>30</td>
<td>15</td>
<td>No difference Improved LR control but no change in OS</td>
</tr>
<tr>
<td>UK multicenter\textsuperscript{40}</td>
<td>NR</td>
<td>468</td>
<td>Non-TME Preoperative RT (15 Gy over 5 d) + non-TME</td>
<td>24</td>
<td>15</td>
<td>No difference Improved LR control but no change in OS</td>
</tr>
</tbody>
</table>

Abbreviations: LR, local recurrence; MRC, Medical Research Council; NR, not reported; OS, overall survival; pCR, pathologic complete response; RT, radiotherapy; TME, total mesorectal excision; UK United Kingdom.
chemoradiation approach is not recommended and should not be used outside the clinical trial setting.

Neoadjuvant continuous-infusion 5-FU or capecitabine used concurrently with 45.0 to 50.4 Gy of radiation in the treatment of LARC, followed by surgery and an additional 4 months of adjuvant fluoropyrimidine, remains today’s standard of care in the United States.

**Future Directions**

The identification of which patients require neoadjuvant chemoradiation and adjuvant chemotherapy, or which patients might benefit from a more aggressive approach with induction chemotherapy, remains an area of intense research. Improved prognostic and predictive markers are sorely needed, and surrogate markers for overall survival, such as pCR rates, require further validation. The final goal of improved complete pCR rates and survival outcomes with neoadjuvant therapy for patients with LARC remains elusive, but several new radiation and systemic strategies show promise.

**Modification of Adjuvant Chemotherapy Based on Pathologic Response to Chemoradiation**

More than 80% of patients who receive preoperative chemoradiation show some degree of tumor regression at surgery, with pCR seen in 15% to 25% of patients.\(^{59,61}\) However, variability exists in the extent of tumor regression, and patients could be classified as having a complete response (ypT0,N0), intermediate response (ypT1–2,N0), or poor response (ypT3–4,N1+). Multiple studies have known shown that pCR is associated with improved local control and survival.\(^{62,63}\) Beets et al\(^{64}\) conducted a large, retrospective, pooled analysis of 2724 patients with either pCR (28%), ypT1–2 (30%), or ypT3–4 (37%) after chemoradiation to determine whether different benefits were seen from adjuvant therapy.\(^{64}\) Patients were followed for a median of 4 years, with 41% of patients administered fluoropyrimidine-based adjuvant therapy. Patients with intermediate tumor response benefited the most from adjuvant therapy, whereas those with pCR or ypT3–4 did not seem to benefit at all. These results suggest that patients with ypT3–4 may be candidates for more intensive therapeutic adjuvant strategies, whereas those with pCR may benefit from omission of adjuvant chemotherapy altogether.

A secondary analysis of the EORTC 22921 trial was performed to determine which subset of patients might benefit from adjuvant chemotherapy after neoadjuvant chemoradiation and surgery.\(^{65}\) The study was limited to 785 of 1011 patients who had undergone an R0 resection. No difference in overall survival was noted, but multivariate analysis showed that adjuvant chemotherapy was associated with significantly improved overall survival in patients who achieved ypT0–2 disease after preoperative therapy compared with patients with ypT3–4 disease. With the caveat that these studies were exploratory in nature and contain only subset analyses with an ad hoc end point, the results show real clinical need and serve as a framework to develop a personalized algorithm for patients with LARC.

**Table 5 Neoadjuvant Chemoradiation in the Treatment of Locally Advanced Rectal Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Arms</th>
<th>pCR (%)</th>
<th>LR (%)</th>
<th>5-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFCD 9203(^{46})</td>
<td>1993–2003</td>
<td>733</td>
<td>Preoperative RT (45 Gy)</td>
<td>3</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative RT + 5-FU</td>
<td>11</td>
<td>8</td>
<td>67</td>
</tr>
<tr>
<td>German study</td>
<td>1995–2002</td>
<td>823</td>
<td>Preoperative RT (50 Gy) + 5-FU</td>
<td>8</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>group(^{48})</td>
<td></td>
<td></td>
<td>Postoperative RT + 5-FU</td>
<td>0</td>
<td>13</td>
<td>74</td>
</tr>
<tr>
<td>EORTC 22921(^{65})</td>
<td>1993–2003</td>
<td>1011</td>
<td>Preoperative RT (45 Gy in 25 fractions)</td>
<td>5.3</td>
<td>17.0</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative RT + postoperative 5-FU</td>
<td>5.3</td>
<td>9.6</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative RT + 5-FU</td>
<td>13.7</td>
<td>8.7</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative RT + 5-FU and postoperative 5-FU</td>
<td>13.7</td>
<td>7.6</td>
<td>65</td>
</tr>
<tr>
<td>NSABP R-03(^{46})</td>
<td>1993–1999</td>
<td>267</td>
<td>Preoperative RT (50 Gy) + 5-FU/leucovorin</td>
<td>15</td>
<td>11</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postoperative RT + 5-FU/leucovorin</td>
<td>0</td>
<td>11</td>
<td>65</td>
</tr>
</tbody>
</table>

Abbreviations: LR, local recurrence; OS, overall survival; pCR, pathologic complete response; RT, radiotherapy.
Preoperative Induction Chemotherapy Integrating Oxaliplatin

Although combining oxaliplatin with neoadjuvant chemoradiation was associated with toxicity and added no benefits, induction chemotherapy before chemoradiation produced some interesting findings. A randomized phase II trial comparing 2 cycles of induction mFOLF-OX6 and long-course chemoradiation versus chemoradiation alone in 57 Belgian patients showed manageable toxicity associated with the induction approach but no significant change in pathologic response rates. However, sphincter preservation rates showed a trend favoring induction chemotherapy (100% vs 67%; P = .058).66 A second randomized phase II trial showed improved tolerance of CAPOX (capecitabine and oxaliplatin) in the neoadjuvant versus adjuvant setting but no change in pathologic response rates or 3-year survival. This trial was confounded by integration of concurrent CAPOX-based radiotherapy.67

The United Kingdom phase II single-arm EXPERT study added 12 weeks of CAPOX induction before capecitabine-based chemoradiation.68 In this trial, the 105 poor-risk patients (defined by high-risk findings on MRI) then proceeded to TME followed by 12 weeks of adjuvant capecitabine, with a primary end point of pathologic response rate. The trial results showed that the pCR was only 20%, equivalent to that obtained with preoperative 5-FU chemoradiation alone. Interestingly, a radiologic response to induction chemotherapy was seen in 74% of patients, increasing to 89% after completion of chemoradiation. The 3-year progression-free and overall survivals were 68% and 83%, respectively. Overall, these results showed that induction chemotherapy could be tolerably administered, but some of intermediate-range outcomes are interesting and will need prospective confirmation. Additional retrospective series have documented promising tumor regression and survival outcomes with mixed results. The key remains in identifying the high-risk subset that would benefit from oxaliplatin-based induction chemotherapy.

Toxicity-Minimizing Strategies

To address the question of whether improved systemic therapy can replace neoadjuvant chemoradiation in the era of TME, the ongoing phase II/III randomized PROSPECT study of patients with T2N1/T3N0–1 rectal adenocarcinoma will assess a treatment algorithm entailing either standard neoadjuvant chemoradiation with adjuvant chemotherapy or 12 weeks of initial FOLFOX with chemoradiation reserved for patients experiencing no response to neoadjuvant chemotherapy (ClinicalTrials.gov identifier: NCT01515787). Potential benefits of this strategy include avoidance of long-term radiation complications, such as bowel and erectile dysfunction.

Sphincter-Preservation Surgery

Sphincter-preservation surgery should be considered for patients with a functioning sphincter and rectal cancer more than 2 cm proximal to the dentate line. Temporary diverting loop ileostomy is used to minimize early postoperative complications. Some experienced centers are encouraging

Table 6 Oxaliplatin-Based Chemoradiation Therapy for Locally Advanced Rectal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Surgery</th>
<th>Preoperative Treatment</th>
<th>pCR (%)</th>
<th>Grade 3 or 4 Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR-0154</td>
<td>747</td>
<td>TME</td>
<td>RT 50 Gy + 5-FU CI</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 50 Gy + 5-FU + oxaliplatin</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>ACCORD1257</td>
<td>598</td>
<td>TME</td>
<td>RT 45 Gy + capecitabine</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 45 Gy + capecitabine + oxaliplatin</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>NSABP R-0455</td>
<td>1606</td>
<td>TME</td>
<td>RT 50 Gy + 5-FU</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 50 Gy + capecitabine</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 50 Gy + 5-FU + oxaliplatin</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 50 Gy + capecitabine + oxaliplatin</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>CAO/ARO/AIO-0448</td>
<td>1265</td>
<td>TME</td>
<td>RT 50 Gy + 5-FU</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 50 Gy + 5-FU + oxaliplatin</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>PETACC-6</td>
<td>1090</td>
<td>TME</td>
<td>RT 50 Gy + 5-FU + oxaliplatin</td>
<td>Results pending</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 45 Gy + capecitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT 45 Gy + capecitabine + oxaliplatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, continuous infusion; pCR, pathologic complete response; RT, radiotherapy; TME, total mesorectal excision.
sphincter preservation in selected patients with a tumor less than 2 cm proximal from the dentate line after response to chemoradiation. However, an unplanned subset analysis of low-lying tumors from the updated German CAO/ARO/AIO-94 trial showed a 10-year local failure rate as high as 12% in patients undergoing abdominal perineal resection even with preoperative chemoradiation,

raising concern that these strategies might further compromise local control. Tumors of the middle and lower third of the rectum are usually managed with low anterior resection with TME. Neorectum function after anterior resection varies according to the level of anastomosis but may improve with the routine use of a colonic reservoir in patients with tumors of the mid or lower rectum.

**Targeted Therapies**

Cetuximab/panitumumab and bevacizumab have been approved for use in patients with metastatic colorectal cancer. Naturally, these agents are currently being investigated in phase I and II clinical trials. Cetuximab used with capecitabine-based chemoradiotherapy showed poor pCR rates in 2 independent phase II trials.

In addition, the rates of grade 3/4 toxicities were higher in the patients who received cetuximab along with capecitabine. Cetuximab has also been used with irinotecan along with capecitabine-based chemoradiotherapy in a phase I trial, resulting in a pCR rate of 25%. Combining cetuximab with oxaliplatin as part of capecitabine-based chemoradiation did not significantly improve pCR rates compared with the 5-FU alone approach (9% vs 20%).

Finally, in the EXPERT-C trial, cetuximab was also evaluated in patients who were undergoing induction chemotherapy.

A total of 165 patients received CAPOX induction therapy followed by capecitabine chemoradiation with or without cetuximab. The patients also received postoperative CAPOX with or without cetuximab after a TME. The use of cetuximab in patients with wild-type K-ras did not improve the primary end point of pCR or progression-free survival. However, an improvement was seen in the response rates and 3-year overall survival (HR, 0.27; \( P = .034 \)) when patients received cetuximab (81% vs 96%). In contrast to the EXPERT-C trial, a recently published pooled analysis of the IRIX and ERBINIX trials showed that adding cetuximab to irinotecan/capecitabine with chemoradiation did not improve clinical outcomes in patients with wild-type K-ras compared with those undergoing chemoradiation without cetuximab.

Bevacizumab has been tested in various phase I and II trials in patients with locally advanced rectal cancer. In most of the trials, the pCR rates have been between 18% and 36%, but a noticeably increased risk of grade 3 and 4 adverse events was seen, including postoperative wound-healing complications.

Unger et al showed that adding celecoxib to capecitabine led to potentially improved efficacy (pCR rate of 25%) and reduced toxicities in the treatment of locally advanced rectal cancer. Additional studies are need to confirm the role of celecoxib as a radiation sensitizer, although a randomized phase III study supports the earlier observation that celecoxib reduced capecitabine-induced hand and foot syndrome.

In summary, the use of targeted agents (anti–epidermal growth factor receptor or vascular endothelial growth factor) with standard chemoradiation did not produce improved outcomes but increased toxicity. Thus, these agents are not to be used in routine clinical use outside of a clinical trial. HER2-targeted agents and vaccines represent a possible unexplored approach in the perioperative setting. Newer agents are being tested in the metastatic setting and, if positive, will need to be integrated into neoadjuvant early-phase trials in selected patient populations.

**Biomarker-Driven Strategies**

Tan et al reported promising results in a prospective single-institution phase II trial based on good or poor risk genotypes of germline thymidylate synthase. Patients with poor-prognosis genotypes (27%) were treated with the addition of irinotecan, 50 mg/m² weekly during 5-FU–based chemoradiation. Despite poorer-risk genotypes, patients treated with concurrent irinotecan showed an impressive 35% pCR rate compared with 19% in good-risk participants. However, grade 3/4 toxicity rates were 25% higher in the irinotecan-treated arm. Use of gene profiling in pretreatment rectal cancer biopsies may assist in predicting treatment response in 83% of the patients. Whether next-generation integrated gene array and the genome atlas can boost the accuracy and guide treatment selection remains to be seen.

Quantification of CSCs in the tumor tissues or in peripheral blood may provide additional tools for treatment outcome predictions and intervention.
The Role of Intensity-Modulated Radiation Therapy in Neoadjuvant Chemoradiation

Intensity-modulated radiation therapy (IMRT) holds promise for decreased toxicity and an improved toxicity profile. Samuelian et al. suggested that IMRT is associated with decreased grade 2/4 gastrointestinal toxicity compared with standard chemoradiation (48% vs 62%; P=.006), with the caveat that this is a retrospective analysis. Although pCR rates were unchanged, long-term toxicity and efficacy data remain to be determined. The Radiation Therapy Oncology Group has recently completed a phase II trial using capecitabine, oxaliplatin, and IMRT-based radiation therapy for patients with rectal cancer, with final results pending (RTOG 0822). Despite an absence of randomized and limited prospective phase II clinical data demonstrating efficacy or decreased toxicity, IMRT is frequently integrated into standard practice. In the opinions of the authors, IMRT should be used selectively in the treatment of patients with rectal cancer.

Conclusions

Despite decreased local recurrence rates, overall survival outcomes for patients with LARC have not significantly improved with the current multimodality therapy over the past decade. Continuous-infusion 5-FU or oral capecitabine remains the backbone of neoadjuvant chemoradiation and adjuvant therapy. Recent research efforts to integrate newer cytotoxic drug or targeted agents did not lead to improved outcomes but rather added toxicities. Future efforts should aim at accurately predicting patients who achieve pCR and sparing them surgery based on modern molecular and imaging techniques. Future efforts should also aim at producing pCR in patients who are destined to experience disease progression on the current standard chemoradiation. These new treatment algorithms will allow clinicians to better select patients and adjust treatments based on risk with the goal of controlling local distant metastases while minimizing toxicities.

References


