Evolving Treatment Options and Future Directions for Locally Advanced Rectal Cancer

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Abstract

Locally advanced rectal cancer can be biologically heterogeneous, but imaging advances have improved clinical assessment of primary tumor and involved lymph nodes in relation to pelvic structures and intended surgical planes. Contemporary treatment for rectal cancer is tailored to the individual patient through multidisciplinary collaboration among diagnosticians, surgeons, medical oncologists, and radiation oncologists to minimize local recurrence and distant metastases. Furthermore, patient preferences and quality of life preservation are becoming more relevant in the decision-making, and upcoming treatment strategies specifically are designed to minimize toxicities and long-term morbidity. Accumulating data have continued to support the use of total neoadjuvant therapy, namely the completion of: (1) multiagent cytotoxic chemotherapy; and (2) pelvic radiation with or without a radiosensitizing agent, before surgery. The total neoadjuvant therapy strategy not only eliminates potentially occult metastases early but also opens up the possibility of nonsurgical management for those who decline or are unfit for surgery. Finally, noncytotoxic agents in combination with established chemotherapy agents along with potentially predictive biomarkers are also being actively investigated to further improve the clinical outcomes of rectal cancer.

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Introduction

Colorectal cancer is the third most common cancer in the world, and rectal cancer accounted for approximately 704,376 cases and 310,394 deaths annually across the world in 2018.[1] Distribution of rectal cancer diagnosis and disease course patterns can vary greatly throughout the world, because of diverse diet and lifestyle, quality of screening programs, and available treatment options. In contrast to colon cancer, locally advanced rectal cancer presents particular management challenges because of the complex anatomy, with close proximity to genitourinary structures, and lymphatic drainage and blood supply beyond the portal circulation. For these reasons, extensive research efforts have focused on producing detailed images of rectal cancer, minimizing rates of residual disease, local recurrence, and distant spread, and finally to identify novel therapeutic targets unique for rectal cancer.

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Standard Preoperative Chemoradiation

Resectable stage II and III rectal cancer is managed differently from colon cancer, largely because of the distinct locoregional recurrence pattern. Multidisciplinary collaboration among gastroenterologists, surgeons, radiation oncologists, diagnostic radiologists, pathologists, and medical oncologists are especially important to accurately stage patients, to assess treatment response, and to optimize multimodality treatment options that include radiation, chemotherapy, and surgery.

The conventional treatment paradigm with preoperative chemoradiation with fluoropyrimidine was first confirmed through the German Rectal Cancer Study Group, which compared preoperative chemoradiation used with 5-fluorouracil with postoperative chemoradiation. The landmark study showed a statistically significant absolute 7% decrease (13% vs. 6%) in 5-year local relapse in the initial analysis and absolute 3% decrease in 10-year local relapse (10% vs. 7%) in the updated analysis.[2,3] However, both arms showed similar long-term survival and proportion of distant metastases (30%). The National Surgical Adjuvant Breast and Bowel Project R-03 study from the United States used a similar treatment strategy and showed a 5-year disease-free survival (DFS) advantage (65% vs. 53%) and at least a trend toward 5-year overall survival (OS) benefit (75% vs. 66%; $P = .07$).[4] Capecitabine, an oral fluoropyrimidine, also showed a noninferior 3-year DFS (76% vs. 67%), an accepted surrogate end point to OS, compared with 5-fluorouracil used with

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Table 1 Expected Rates of pCR and Serious Adverse Events of Concurrent Chemoradiation From Phase III Randomized Controlled Trials for Resectable Rectal Cancer

Name of Trial	Sample Size	Cytotoxic Agent Used with Concurrent Radiation	pCR, %	Grade ≥3 Adverse Events Per CTCAE, %	Reference
CAO/ARO/AIO-94 (Germany)[a]	415	5-FU	8	27	2
NSABP R-03 (United States)[a]	123	5-FU	15.0	52	4
ACCORD 12/0405-Prodige 2 (France)	584	Capecitabine	13.9	11	7
		CAPOX	19.2	25	
STAR 01 (Italy)	747	5-FU	16.4	8	8
		FOLFOX	16.0	24	
NSABP R-04 (United States)	1556	5-FU or capecitabine	17.8	27-30	10
		FOLFOX or CAPOX	19.5	40-42	
FOWARC (China)	483	5-FU	14.0	NA	11
		FOLFOX	27.5	NA	
		FOLFOX (no radiation)	6.6	NA	
PETACC-6 (Europe)	1094	Capecitabine	11.5	15	12,13
		CAPOX	13.0	38	

Abbreviations: ACCORD = Actions Concertées dans les Cancers Colorectaux et Digestifs; CAO/ARO/AIO-94 = Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society; CAPOX = capecitabine and oxaliplatin; CTCAE = common terminology criteria for adverse events; FOLFOX = 5-fluorouracil and oxaliplatin; FOWARC = Neoadjuvant FOLFOX6 Chemotherapy With or Without Radiation in Rectal Cancer; 5-FU = 5-fluorouracil; NSABP R = National Surgical Adjuvant Breast and Bowel Project; pCR = pathologic complete response; PETACC = Pan-European Trials in Adjuvant Colon Cancer; STAR = Studio Terapia Adiuvante Retto.
[a]Compared with postoperative chemoradiation group.

preoperative chemoradiation in Germany.[5] Capecitabine, as an oral drug, is considered more convenient because 5-fluorouracil requires continuous intravenous infusion. Thus, a common standard of care treatment for rectal cancer, especially in North America, has become preoperative chemoradiation with capecitabine for 5 to 6 weeks followed by surgical resection.

After the evidence for single-agent fluoropyrimidine, there have been global efforts to maximize chemoradiation through concurrent multiagent chemotherapy, most of which disappointingly revealed no definite survival advantage. First, the ACCORD (Actions Concertées dans les Cancers Colorectaux et Digestifs) 12 trial from France showed no improvement in local relapse, DFS, or OS with the additional use of CAPOX (oxaliplatin and capecitabine) with concurrent radiation before surgery.[6,7] Second, the STAR (Studio Terapia Adiuvante Retto) 01 study from Italy reported similar findings; however, they also reported that the additional use of FOLFOX (oxaliplatin and 5-fluorouracil) with concurrent radiation increased toxicities (serious adverse events, 24% vs. 8%).[8,9] Table 1 shows the increased proportion of serious adverse events observed in chemoradiation groups with multiagent chemotherapy compared with single-agent chemotherapy and the modest pathologic complete response (pCR) rate, an immediate surrogate end point at the time of surgery, across well known randomized controlled trials (RCTs) globally.[2,4,7,8,10-13] Likewise, the US NSABP R-04 study, in which either FOLFOX or CAPOX combination with radiation was compared with single-agent fluoropyrimidine with radiation, similarly reported no difference in local relapse (oxaliplatin: 11% vs. no oxaliplatin: 12%; $P = .70$), 5-year DFS (69% vs. 64%; $P = .34$), and 5-year OS (81% vs. 79%; $P = .38$).[10,14] Therefore, preoperative chemoradiation with single-agent fluoropyrimidine, not FOLFOX or CAPOX, has remained the standard of care.

In recent years, the treatment of rectal cancer has shifted toward establishing strategies that could minimize toxicities, especially because intensified therapy has failed to improve survival. The German Rectal Cancer Study Group recognized that high-quality resection of rectal cancer was vital to minimizing the rate of local recurrence.[15] With modern surgical techniques and wide adoption of total mesorectal excision (TME), the value of rectal cancer radiation is being questioned in select rectal cancer cases for which the anticipated local recurrence is low. The risk of local recurrence is on the basis of rectosigmoid location, depth of primary tumor away from surgical margins, or limited or absent lymph node involvement. In fact, the relationship of rectal cancer to the circumferential margin (CRM) on pathology is associated with local recurrence, as high as 43% in involved or at least "threatened" margins compared with recurrence of 8%, if CRM was uninvolved.[16] The FOWARC (Neoadjuvant FOLFOX6 Chemotherapy With or Without Radiation in Rectal Cancer) 3-arm RCT from China specifically asked this question. The study showed no difference in local relapse (10% vs. 9% vs. 9%) or 3-year DFS (76% vs. 78% vs. 76%) in a comparison of radiation with 5-fluorouracil (conventional), radiation with FOLFOX, and FOLFOX without any radiation, although the rates of pCR at time of surgery were lower without radiation (14% vs. 28% vs. 7%).[11,17] The ongoing randomized PROSPECT (Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery) trial (NCT01515787) from the United States and Canada will address whether pelvic radiation could be spared for select patients with low-risk stage II or III rectal cancer (T2N1, T3N0, and T3N1) if they were to receive preoperative chemotherapy with FOLFOX and show no disease progression and estimated tumor regression of at least 20% after 6 cycles of FOLFOX.[18] The caveat is that patients with high risk of local relapse, such as clinical T4 disease, N2 disease, low rectal tumors (ie, close to anal verge), or involved CRM, are excluded from study enrollment because previous RCTs have already shown clinical

Table 2 Observed Long-Term Survival and Treatment Compliance of Adjuvant Chemotherapy From Randomized Controlled Trials for Resected Rectal Cancer

Name of Trial	Sample Size	Endpoint Type	Adjuvant Chemotherapy Regimen	Endpoint Result, %	Percent Started	Percent Completed	Reference
CAO/ARO/AIO-94 (Germany)[a]	395	10-Year OS	5-FU with radiation	60	72	56	2,3
NSABP R-03 (United States)[a]	131	5-Year OS	5-FU with radiation	66	76	NA	4
EORTC 22921 (Europe)	1011	10-Year OS	5-FU	52	73	66	22,23
			Observation	48	NA	NA	
PETACC-6 (Europe)	1094	7-Year OS	CAPOX	74	75	57	12
			Capecitabine	74	80	69	
ADORE (South Korea)	321	6-Year OS	FOLFOX	78	91	88	24
			5-FU	76	93	88	
Chronicle (United Kingdom)	113	3-Year OS	CAPOX	89	93	48	25
			Observation	88	NA	NA	

Abbreviations: ADORE = Adjuvant Chemotherapy After Preoperative Chemoradiotherapy to Treat Rectal Cancer; CAO/ARO/AIO-94 = Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society; CAPOX = capecitabine and oxaliplatin; EORTC = European Organization for Research and Treatment of Cancer; FOLFOX = 5-fluorouracil and oxaliplatin; 5-FU = 5-fluorouracil; NSABP R = National Surgical Adjuvant Breast and Bowel Project; OS = overall survival; PETACC = Pan-European Trials in Adjuvant Colon Cancer.
[a]Compared with preoperative chemoradiation rather than a control group.

benefit in this patient population. For these patients, local recurrence, especially among iliac and obturator compartments, remains a problem even after optimal surgery and chemoradiation, sometimes requiring more morbid "salvage" surgeries.[19,20] Therefore, high rectal tumors (ie, rectosigmoid) with low risk of recurrence could be treated more like "colon cancer" without radiation, but classic and bulky rectal cancer would undergo more intensive treatment strategies.

From Adjuvant to Preoperative Chemotherapy

Controversies persist regarding adjuvant chemotherapy in rectal cancer because the original landmark MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study did not enroll patients with rectal cancer.[21] Furthermore, the European Organization for Research and Treatment of Cancer 22921 study did not show a difference in long-term DFS or OS with adjuvant chemotherapy compared with observation in rectal cancer.[22,23] Table 2 shows similar long-term OS between randomized arms of important adjuvant chemotherapy trials but also notes the lack of treatment adherence that limited some of these trials' ability to detect clinical benefit.[2-4,12,22-25] The PETACC (Chemotherapy and Radiation Therapy Before Surgery Followed by Capecitabine With or Without Oxaliplatin in Treating Patients With Locally Advanced Rectal Cancer)-6 study from Europe similarly reported no survival advantage with adjuvant oxaliplatin-based chemotherapy after preoperative chemoradiation and surgery.[12] However, surgical morbidity and slow postoperative recovery have possibly prevented approximately 50% from receiving optimal doses of adjuvant chemotherapy in these respective trials,[3,22] thereby resulting in no difference in OS (Table 2). The time point of randomization for these trials occurred before preoperative treatment, which made studying adjuvant chemotherapy difficult if patients developed complications related to preoperative radiation or surgical resection. In the most recent adjuvant phase II RCT (ADORE [Adjuvant Chemotherapy After Preoperative Chemoradiotherapy to Treat Rectal Cancer]) from South Korea, smartly patients were randomized after preoperative chemoradiation and curative surgery, and thus a 6-year DFS advantage (68% vs. 57%; hazard ratio, 0.63; 95% confidence interval [CI], 0.43-0.93) could be shown, but still no convincing OS benefit with adjuvant FOLFOX compared with fluoropyrimidine alone in an optimal treatment adherence setting.[24,26]

Even so, in a systematic review from the Cochrane Library a 17% reduction from death (hazard ratio, 0.83; 95% CI, 0.76-0.91, for OS) was convincingly shown when any adjuvant fluoropyrimidine-based chemotherapy was compared with observation after surgery across 21 RCTs and 16,215 patients.[27] All in all, up to 4 months of combination chemotherapy, either FOLFOX or CAPOX, has been clinically extrapolated for adjuvant treatment of resectable stage II and III rectal cancer after preoperative chemoradiation (5-6 weeks) and surgery in the United States.

Trial limitations for adjuvant chemotherapy have been commonly summarized to be due to suboptimal staging and diagnostic imaging, poor adjuvant treatment adherence, and surgical complications resulting in a delay of adjuvant therapy.[28] Clinicians certainly have not abandoned the concept of combination chemotherapy for rectal cancer. A subsequent retrospective study surprisingly identified adjuvant chemotherapy to be associated with survival benefit even in patients who achieve pCR (5-year OS of 95% vs. 88%).[29] This could be explained by the fact that pCR in conventional chemoradiation could be related to pelvic radiation effect, and so combination chemotherapy could still be helpful to eliminate distant occult metastatic disease. Patients who achieve a pCR at the time of surgery, nevertheless, have a favorable prognosis, with 5-year OS of 93% compared with 73% in other patients according to a meta-analysis.[30] As a result, moving FOLFOX or CAPOX chemotherapy to before surgery has gained attraction because this strategy, known as total neoadjuvant therapy (TNT), increases treatment compliance, allows better tolerability of chemotherapy, and increases the rates of pCR.[31,32] Patients who have completed preoperative chemoradiation with single-agent fluoropyrimidine followed by preoperative FOLFOX could achieve pCR as high as 38% at the time of surgery,[33] whereas those given

Table 3 Pathologic CR of TNT for Rectal Cancer in Select Large Cohort or Interventional Studies

Name of Study	Sample Size of Response Assessment	TNT Regimen	pCR, %	Reference
Retrospective Study From MSK in the United States	308	Induction chemotherapy with FOLFOX or CAPOX followed by chemo-RT	35.7	31
Timing of Rectal Cancer Response to Chemoradiation Consortium Phase II Study From the United States and Canada	67	Chemo-RT followed by FOLFOX 2 cycles	25.4	33
	67	Chemo-RT followed by FOLFOX 4 cycles	29.9	
	65	Chemo-RT followed by FOLFOX 6 cycles	38.5	
COPERNICUS Phase II Study From the United Kingdom	57	FOLFOX 4 cycles followed by short-course radiation	12.3	36
Polish Colorectal Study Group Phase III Study	261	Short-course radiation followed by FOLFOX 3 cycles	16	37
Royal Marsden Hospital Rectal Cancer Study Group Phase II Study From the United Kingdom and Australia	105	CAPOX 4 cycles followed by chemo-RT	20	38
Grupo Cáncer de Recto 3 Phase II Study From Spain	56	CAPOX 4 cycles followed by chemo-RT	14.3	39
EXPERT-C Phase II Study From Europe	81	CAPOX 4 cycles followed by chemo-RT	8.6[a]	40
	83	CAPOX with cetuximab 4 cycles followed by chemo-RT	10.8[a]	

Abbreviations: CAPOX = capecitabine and oxaliplatin; chemo-RT = chemoradiation; COPERNICUS = chemotherapy then radiation then immediate curative surgery for operable rectal cancer; EXPERT-C = multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer; FOLFOX = 5-fluorouracil and oxaliplatin; MSK = Memorial Sloan Kettering Cancer Center; pCR = pathologic complete response; TNT = total neoadjuvant therapy.
[a]Radiologic complete response.

conventional chemoradiation have an expected pCR of only 13% to 17%.[30,34,35] Table 3 shows the expected rates of pCR reported from large studies that incorporated preoperative combination chemotherapy and chemoradiation (or short-course radiation), or namely, TNT.[31,33,36-40] The exact duration of an oxaliplatin-based chemotherapy regimen (FOLFOX or CAPOX) and its sequence either before or after conventional preoperative chemoradiation have not been securely established. Such a treatment strategy does also allow for "short-course radiation" with higher radiation dose per fraction before or after combination chemotherapy, which is more widely accepted and more actively investigated in Europe.[36] Preoperative short-course radiation for rectal cancer was compared with long-course radiation in the Stockholm III RCT with similarly low rates of local recurrence,[41] but it is less clear as to how this could be sequenced with preoperative chemotherapy. Immediate surgery within 1 week after short-course radiation also might lead to less pathologic downstaging compared with long-course radiation.[41] The RAPIDO (Rectal Cancer and Pre-operative Induction Therapy Followed by Dedicated Operation) trial in Europe is an eagerly awaited phase III study (NCT01558921) that compared short-course radiation and CAPOX with conventional long-course chemoradiation. Surgery was planned 4 to 6 weeks after TNT in this trial to allow pathologic downstaging and adequate treatment recovery.[42] In summary, versions of upfront TNT with surgery as the last stop are becoming an increasingly accepted standard of care.

Nonsurgical Management

Although perfecting high-quality TME techniques have decreased disease relapse, efforts globally have also been to minimize perioperative and postoperative morbidities. Laparoscopic resection, which can shorten hospital stay by at least 1 day, has shown survival outcome similar to the open procedure (3-year DFS of 74% vs. 71%; 3-year OS of 87% vs. 84%) in an RCT of 1044 patients,[43] although some RCTs have observed higher rates of close or involved surgical margins.[44,45] Faster and easier recovery from surgery logically could increase compliance with subsequent adjuvant therapies. Endoscopic mucosal resection is also being investigated for earlier-stage rectal cancer, but this minimally invasive technique does not address the problem of local and lymphatic spread inherent in rectal tumors. Although local mucosal excision failed to show better clinical outcomes compared with standard TME in most patients,[46] select patients with node-negative rectal cancer could benefit from local excision after application of TNT.[47]

Another treatment strategy is to consider no immediate surgery after chemotherapy and radiation. With the progressive adoption of TNT, an increasing proportion of patients are achieving clinical complete response according to imaging and clinical exam, thus bringing into question the role of surgery in such cases. Therefore, nonsurgical management is now incorporated in a phase II RCT in which the sequence of preoperative combination chemotherapy and conventional chemoradiation (NCT02008656) are being compared.[48] Recent reports have indicated that nonsurgical management of newly diagnosed rectal cancer in the United States has also increased from 2.4% in 1998 to 5% in 2010 according to the National Cancer Database.[49] These practice patterns suggest that for select patients with specific disease state, comorbidities, and life goals, a nonsurgical option is being used even outside clinical trial settings. Accumulating data from a large observational study of 880 patients has established that well-selected patients who achieve clinical complete response from neoadjuvant therapy and who opt for nonsurgical management initially could maintain 5-year OS of 85% and 5-year DFS of 94%.[50] Local recurrence has been estimated as high as 21% to 34%, but they often could be salvaged with local excision or standard TME.[50-52] In a retrospective study of 259 patients with clinical complete response from chemoradiation in the United Kingdom, the 3-year colostomy-free survival, a patient-oriented

outcome, was 74% in the no immediate surgery cohort compared with 47% in the immediate resection cohort.[52] Despite the potential clinical benefit to patients, to date, there have not been any RCTs that have compared these 2 interventions (surgery vs. no surgery) head to head. Even so, other retrospective cohort studies also have noted no difference in OS, even with analysis adjusted for relevant baseline factors, between initial nonsurgical management versus immediate surgery among those who achieved clinical complete response.[53,54] Ongoing organ preservation trials (NCT03561142 from Germany, NCT02008656 from the United States and Canada, NCT02514278 from France, NCT03565029 from Italy, NCT03426397 from Belgium and Netherlands, and NCT02860234 from China) are aimed at developing preoperative treatment regimens and sequences that can increase clinical complete responses to make nonsurgical management a more viable option. Such treatment strategy, nevertheless, has been criticized and might be associated with worse survival in an unselected real-world population with higher-risk stage II and III rectal cancer according to population data from the National Cancer Database.[55] Thus, despite the promise, it still remains difficult to recommend organ preservation outside of the auspices of a clinical trial.

Magnetic resonance imaging (MRI) is rapidly becoming the standard imaging tool to provide accurate clinical staging with high sensitivity of 0.97 and specificity of 0.97 regarding the degree of tumor invasion,[56] compared with a wide range of sensitivity (0.69-0.91) seen with endoscopic rectal ultrasound imaging.[57] By establishing the location and invasion of the primary tumor and any pathologic lymph nodes, the risk of disease recurrence and involved margin, as well as the extent of surgery, could be estimated. This clinical information can help clinicians and patients to make informed decisions regarding: (1) conventional chemoradiation followed by surgery and possible adjuvant chemotherapy; (2) TNT with chemoradiation and combination chemotherapy; and (3) organ preservation strategies. Subsequent MRI used to monitor treatment response has also been correlated with survival.[58] Response to radiation and response to chemotherapy shown on MRI scans can be particularly helpful to understand the risk of disease relapse, especially for nonsurgical management for which there would not be further pathologic information. MRI might also be more convenient than endoscopic rectal ultrasound imaging or endoscopic procedures that require sedation, although expertise in performing and reading high-quality rectal protocol MRI is required. Future studies investigating new therapeutic agents for TNT will likely continue to use MRI and other highly sensitive imaging techniques to grade treatment response. Novel image-based surrogate end points could accurately gauge the need for surgical resection, especially at a time when serum biomarkers such as circulating tumor DNA have not yet been established for use in early-stage colorectal cancer.[59] However, active research and clinical validation of such biomarkers will likely complement imaging technology in the near future.

Future Directions and Translational Research

Immune- and biomarker-driven therapy that might predict or guide treatment response has gained recent attention. Checkpoint inhibitors are approved by the US Food and Drug Administration for colorectal cancer with high microsatellite instability (MSI-high). However, MSI-high rectal cancer has good prognosis with conventional trimodality treatment, with one study showing 5-year DFS of 100% for stage II and 85% for stage III rectal cancer.[60] Furthermore, most rectal cancers are microsatellite-stable, as a molecular subtype profiling study of 1876 patients showed, that rectal cancers are more likely to harbor *TP53* (69%) and *KRAS* mutations (51%) and are less likely to be MSI-high (2%).[61] For MSI-stable rectal cancer patients, although more is needed to understand how to augment the immune response, an ongoing phase II trial is ongoing on the use of durvalumab, an anti-programmed death ligand 1 (PD-L1) checkpoint inhibitor, after conventional chemoradiation (NCT03102047). However, it remains to be determined if chemoradiation could be a strategy to improve response to checkpoint inhibitors although preclinical data might suggest this and thus remains a new area of ongoing investigation.

Treatment with neoadjuvant chemoradiation has been associated with the generation of unique somatic mutations as well as upregulation of genes involved in the immune response pathways, leading to immune activation and enhanced treatment response.[62] It is widely hypothesized that radiation could increase treatment response to checkpoint inhibitors. Biomarkers developed of reactive oxygen species as a marker of DNA damage from radiation treatment have been associated with response to conventional chemoradiation treatment.[63] Perhaps DNA damage and high mutational load could help create an environment where ample tumor antigens are more readily presented to immune cells that could be activated by checkpoint inhibitors, but these mechanisms still need to be elucidated. The National Cancer Institute is currently sponsoring a randomized phase II trial (NCT02921256) to test the concept of conventional chemoradiation with capecitabine used with veliparib, a poly adenosine diphosphate ribose polymerase inhibitor that blocks DNA repair, and capecitabine with pembrolizumab (anti-programmed death 1 inhibitor). Trifluridine/tipiracil-102, an oral fluoropyrimidine with fewer gastrointestinal and dermatologic side effects than capecitabine, is being studied as a novel radiosensitizing agent in chemoradiation for rectal cancer as well (NCT03297710). Furthermore, another commercially available assay, PD-L1 expression, might also be a relevant biomarker that is associated with increased CD8 T-cell density and response to immunotherapy.[64] Infiltrating T cells has been one of the more reliable markers for response and survival including for rectal cancer treated with chemoradiation.[65] All in all, further examination of novel radiosensitizing agents and immunotherapy combinations that might improve pathologic and radiographic responses in rectal cancer, is necessary to optimize TNT and nonsurgical management.

Conclusions

Exciting research in rectal cancer is moving away from conventional trimodality treatment with chemoradiation, and surgery, followed by adjuvant chemotherapy to TNT, and novel targeted and immunotherapy agents are being incorporated. Research to optimize treatment outcomes for patients who are unlikely to benefit from or have reservation regarding rectal cancer radiation or surgery is currently ongoing. Imaging advances along with biomarker development are especially important in carefully

selecting and monitoring patients who undergo these less conventional strategies. Finally, novel immunotherapy and targeted agents might also improve clinical outcomes and minimize treatment-related toxicities.

Disclosure

The authors have stated that they have no conflicts of interest.

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