Current Colorectal Cancer Reports (2021) 17:1–9
https://doi.org/10.1007/s11888-020-00462-3

SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Review and Updates on Approaches to Neoadjuvant Chemotherapy in Rectal Cancer

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Accepted: 26 December 2020 / Published online: 16 January 2021

Abstract

Purpose of Review The currently established standard of care treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and adjuvant fluorouracil and oxaliplatin. The body of evidence that supports this treatment has grown over the last 20 years. However, recent advances and ongoing studies seek to further evaluate the role of neoadjuvant chemotherapy with and without radiation and total neoadjuvant therapy (TNT). In this article, we review the current literature as well as investigate the emerging role of TNT for patients with LARC and comment on updates utilizing combination neoadjuvant chemotherapy in early-stage rectal cancer.

Recent Findings Evidence for the current standard of neoadjuvant CRT comes from well-established randomized phase III trials as well as emerging evidence on merits of TNT. There is a growing body of literature including retrospective analysis and ongoing clinical trials that look at upfront induction chemotherapy in addition to CRT prior to surgical resection leading to more effective delivery of systemic therapy and increases in response to treatment. Neoadjuvant combination chemotherapy is also being investigated in early-stage low rectal tumors to see if rates of local excision will increase compared to radical excision.

Summary Current evidence continues to support neoadjuvant CRT as the standard treatment for LARC. There is an increasing body of evidence to support TNT in LARC as an effective treatment strategy that better ensures delivery of systemic therapy leading to higher rates of complete response (CR) and is encouraging for the development of non-operative protocols. There is ongoing evaluation looking at the benefit of novel sensitizers added to neoadjuvant therapy and ongoing investigation into upfront combination chemotherapy with selective use of radiation in upper rectal cancers.

Keywords Rectal cancer · Neoadjuvant · Chemotherapy · TNT

Introduction

Despite advances in screening and treatment modalities over the last 20 years, an estimated 43,340 cases of rectal cancer will be diagnosed in 2020 with colorectal cancer remaining at the third highest incidence and mortality of all cancers in the USA [1]. These statistics continue to highlight the constant need to critically evaluate the current standards of treatment for rectal cancer and investigate novel treatment modalities. Disseminated disease remains the most common cause of death in patients but local recurrence (LR) leads to severe disabling symptoms, is difficult to treat, and is often fatal [2]. Over the last 20 years, the paradigm has shifted to neoadjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) with chemotherapy after surgery [3]. Although such multimodality therapy has markedly reduced local recurrence rates, there remains an estimated 5-year distant relapse rate of 35% representing the leading cause of death in this population [4•]. In many cases, planned adjuvant therapy cannot be fully completed bringing into the question the benefits of receiving a full-planned course of chemotherapy preoperatively. There have been significant advances in systemic chemotherapy for patients with colorectal cancer since 2002 with the introduction of combination regimens. Response rates with modern chemotherapy regimens such as 5-FU, leucovorin, oxaliplatin (FOLFOX) have routinely exceeded 50% and are frequently as high as 60–70% in the advanced setting. More recently, results of induction

This article is part of the Topical Collection on *Systemic Therapies in Colorectal Cancer*

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chemotherapy with CRT prior to surgery have been reported with promising results of higher percentages of completed courses of chemotherapy and higher rates of [4•]. These results have spurred to development of randomized prospective trials utilizing treatment arms separating total neoadjuvant therapy (TNT) and CRT + adjuvant chemotherapy.

Neoadjuvant combination therapy is under active investigation for early-stage rectal cancer as well. TME has been well-established to be a highly effective treatment for this disease with local recurrence of only 3–6% [5]. However, the postoperative mortality for these patients is significant at 3–4% and a permanent ostomy is needed in 25% of cases that is detrimental to quality of life [6]. Ongoing studies are evaluating the role of if upfront systemic therapy can lead to higher rates of rectal preservation in this subgroup.

There has been substantial groundwork leading to the current standard of care treatments for both LARC and early-stage rectal tumors. We will provide updates on novel treatment modalities and investigate updates in TNT for LARC and review ongoing clinical trials and explore the role of neoadjuvant combination chemotherapy for early-stage tumors. In the age of targeted and immunotherapy, a question that should be asked at every turn is what novel drugs and biomarkers can be added with the goal to improve pathologic complete response (pCR) and overall survival (OS).

Current Standard of Care

The standard of care for treatment of stage II and stage III LARC is well-established. Thus far, novel therapies have been ineffective for LARC [7, 8•, 9]. Treatment consists of neoadjuvant CRT followed by TME and adjuvant chemotherapy (fluorouracil- or capecitabine-based) leading to excellent local control with substantially lower rates of local recurrence compared to distant recurrence [10].

The defined regimen consisted of 50.4 Gy in 28 daily fractions concurrent with infusional fluorouracil (FU; 1000 mg/m^2 daily for 5 days during the first and fifth weeks of RT. This was followed by four additional cycles of adjuvant single-agent FU (500 mg/m^2 bolus daily for 5 days every 4 weeks) after TME.

There were three prospective randomized studies running simultaneously to compare the efficacy of neoadjuvant versus adjuvant CRT. These were the RTOG 94-01, NSABP R-03, and the CAO/ARO/AIO-94. Of these the RTOG 94-01 and NSABP R-03 were terminated early due to poor accrual. The German Rectal Cancer Study Group CAO/ARO/AIO-94 trial was completed with updated results reported after a median follow-up of 11 years published in 2012 [11]. Compared with patients randomized to the adjuvant arm, significantly lower rates of 5- and 10-year pelvic relapse (6% vs 13%; P ¼ .006 and 7% vs 10%; P ¼ .048, respectively) were seen in those allocated to neoadjuvant CRT, although there were no significant differences in disease-free survival (DFS) or OS between the 2 groups. Patients receiving neoadjuvant therapy also experienced considerably less acute grade 3 (27% vs 40%; $P < .001$) and chronic toxicities (14% vs 24%; $P < .01$). This established the current standard role of neoadjuvant CRT in stages II and III rectal cancer.

Capecitabine has also been compared to fluorouracil for LARC. Hofheinz et al. sought to show non-inferiority in a randomized, multicenter phase III study with results published in June 2012. This compared the two agents in both the neoadjuvant and adjuvant setting designed to examine non-inferiority of 5-year OS in the capecitabine versus that in the fluorouracil group. With median follow-up of 52 months, the 5-year OS in the capecitabine group was non-inferior to that in the fluorouracil group with HR 76% [95% CI 67–82] vs 67% [58–74]; $P = 0{\cdot}0004$. The number of patients with local recurrences were similar in both groups (12 [6%] in the capecitabine group vs 14 [7%] in the fluorouracil group, $P = 0{\cdot}67$). Notably, there were fewer patients that developed distant metastases in the capecitabine group (37 [19%] vs 54 [28%]; $P = 0{\cdot}04$) [12].

It has been well-validated that preoperative therapy leads to significant tumor downsizing resulting in pathologic complete response (pCR) in a subset of patients and that the pathologic stage (which is heavily influenced by preoperative stage and response to treatment) has been found to be the best predictor of disease-free survival [13]. Prior literature suggests patients that reach pCR have improved recurrence and survival rates [14–17]. A systematic review of 16 LARC studies, compared with patients with residual pathologic disease, those achieving a pCR had significantly fewer local recurrences (odds ratio (OR) 0.25; $P = 0.002$), less frequent distant relapse (OR 0.23; $P < .001$), and higher 5-year DFS (OR 4.33; $P < .001$) [18]. However, multiple phase III trials have failed to validate pCR as an independent prognostic factor of OS. In search of better markers, the neoadjuvant rectal (NAR) score was developed as a short-term surrogate endpoint [19]. The NAR score is a weighted combination of post neoadjuvant therapy nodal stage (ypN) and downstaging of T. It has been tested as a surrogate endpoint in the NSABP R-04 study where it was shown to be closely associated with OS ($P < .0001$) and was a better predictor of OS than pCR ($P < .0001$) [19]. The NAR score has been approved by the National Cancer Institute as an acceptable surrogate primary endpoint in clinical trials assessing the impact of neoadjuvant therapy for rectal cancer.

Current consensus guidelines recommend 4 months of adjuvant fluoropyrimidine-based chemotherapy for all patients with LARC who receive neoadjuvant CRT followed by surgical resection, regardless of surgical pathologic findings [3]. Many studies have been conducted but unable to show benefit of adjuvant therapy in terms of DFS and OS [13]. These results led to the logical concluding question of how to more

effectively implement systemic therapy to improve overall survival in the preoperative setting. Chemotherapy may have dual role in management of rectal cancer as it serves as a radiosensitizer and also tackles circulating micro metastases thus helping control local as well as distant relapses, ultimately prolonging DFS and OS.

Intensification of Therapy

Given the high risk of local and distant relapse associated with LARC, multiple studies have looked at the intensification of neoadjuvant therapy to improve disease control rates.

Chemotherapy as Radiosensitizer

The landmark study by Sauer et al. (CAO/ARO/AIO-94) established role of fluoropyrimidine-based CRT, as the standard of care. Oxaliplatin has activity in advanced colorectal cancer and has radiosensitizing properties, and by the virtue of these properties, its role in neoadjuvant CRT for rectal cancer, in combination with fluoropyrimidine and radiation has been explored extensively. Results from multiple trials adding oxaliplatin to standard CRT have all demonstrated increased toxicity with variable efficacy data but no clear benefit in terms of DFS and OS [20–24]. The NSABP R-04 study demonstrated nearly identical DFS and OS for LARC patients treated with either oral capecitabine or continuous 5-FU as a radiosensitizer. But, the addition of oxaliplatin failed to improve rates of pCR or rectal preservation but was associated with significantly higher rates of overall and grades 3–4 toxicities ($P < .0001$) [25]. The German CAO/ARO/AIO-04 published July 2015 was a multicenter, open-label, phase 3 study that randomly assigned patients to receive fluoropyrimidine-based CRT versus oxaliplatin added to both preoperative CRT and adjuvant chemotherapy. A 3-year DFS was 75.9% in the investigational group and 71.2% in the control group ((HR) 0.79 $P = 0.03$). Significantly more preoperative grades 3–4 toxicities occurred in 144 (24%) of 607 patients who received fluorouracil CRT and oxaliplatin compared with 128 (20%) of 625 patients who received fluorouracil CRT. Late grades 3–4 adverse event (AE) in protocol-specified preoperative and postoperative treatment was 25% of patients in the investigational group and 21% patients in the control group [26].

Irinotecan has also been tested in combination with fluorouracil-based CRT in multiple phase II trials [27–29]. A study by Mohiuddin et al. enrolled 106 patients randomized to either 5-fluorouracil plus pelvic hyperfractionated radiation in arm 1 or 5-fluorouracil plus irinotecan weekly × 4, plus pelvic RT for arm 2. With a median follow-up of 6.4 years in arm 1 and 7.0 years in arm 2, pCR rates of 30% (95% CI 0.17, 0.43) and 26% (95% CI 0.15, 0.38) were observed respectively. Locoregional recurrence rates were similar at 16% in arm 1 and 17% in arm 2. Five-year OS rates were 61% (95% CI: 47%, 74%) in arm 1 and 75% (95% CI: 61%, 85%) in arm 2; however, OS and DFS data were complicated by five unrelated second primaries occurring in patients on arm 1, and 1 s primary occurred in arm 2. Gollins et al. evaluated 110 patients with LARC (high-risk T3 and T4 rectal tumors identified on MRI) in a single-arm phase II study. Radiotherapy was given to 45 Gy in 25 fractions over 5 weeks with concurrent oral capecitabine at 650 mg/m^2 twice per day continuously days 1 through 35 and intravenous irinotecan at 60 mg/m^2 once weekly weeks 1 to 4. Three-year local recurrence-free survival was 96.9%, metastasis-free survival was 71.1%, OS was 88.2%, and DFS was 63.5%. This demonstrated high response rates and promising long-term survival and further suggesting that downstaging to ypCR remained a significant predictor of OS ($P = 0.005$) and may be a short-term surrogate for long-term survival.

The phase III ARISTOTLE study comparing standard CRT with capecitabine- and irinotecan-based CRT has completed accrual and will provide further guidance about the use of irinotecan-based combinations in this setting (ISRCTN09351447) [30•].

Total Neoadjuvant Therapy

There has been an increasing body of evidence to support delivery of systemic chemotherapy in the neoadjuvant setting in addition to CRT. The important goal of this multi-modal approach is to make optimal the delivery of systemic therapy targeting micrometastases. Phase II/III studies that have investigated CRT followed by TME and adjuvant chemotherapy have continued to find mediocre compliance with adjuvant chemotherapy resulting in only 50% of trial patients able to receive the full-planned course of post-surgical treatment most commonly due to toxicity or patient refusal [31].

Chau et al. published the results of a prospective single-arm study in 2006 that evaluated the effect of upfront combination chemotherapy followed by CRT on the rate of radiologic and symptomatic response as well as rate of pCR for patients with MRI-defined poor-risk rectal cancers. Patients received 12 weeks of neoadjuvant oxaliplatin with capecitabine followed by synchronous CRT and TME followed by 12 weeks of adjuvant capecitabine. Pathologic complete response was observed in 16 patients (24%; 95% CI, 14 to 36%), and additionally, 32 patients (48%) had only microscopic tumor foci. Eighty-eight percent of patients had radiologic response after receiving capecitabine/oxaliplatin and 86% had symptomatic responses with a median of only 32 days [32].

One of the early randomized studies to investigate the role of TNT was performed by the Grupo Cancer de Recto 3 by Fernandez-Martos et al. The phase II randomized study

specifically looked at CRT followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) in arm A compared to CAPOX followed by CRT and then surgery in arm B. The rates of pCR were similar between the two groups (13.5% and 14.3% respectively). Notably, CAPOX treatment exposure was significantly higher in arm B compared to that in arm A ($P < 0.0001$). Grades 3–4 toxicities were similar during CRT but significantly higher during postoperative CAPOX in arm A compared with neoadjuvant in arm B [33]. The TNT group showed improved overall compliance. PANEX, a pooled analysis of EXPERT and EXPERT-C trials, the two largest trials of neoadjuvant CAPOX followed by CRT, TME, and adjuvant CAPOX ± cetuximab in MRI-defined, high-risk, LARC was presented at ASCO meeting in 2014. The analysis suggested a radiologic response rate of 62% after neoadjuvant chemotherapy and 80% after CRT. Surgery was performed in 91% and T/N downstaging was achieved in 56%/55% cases, and pCR rate was 19%. After a median follow-up of 69 months, 5-year local control and overall survival were 94% and 73% [34].

Recently reported studies directly compare TNT to CRT and induction versus consolidation chemotherapy prospectively. PRODIGE-23 is a phase III multicenter open-label randomized 2-arm phase III superiority trial by Conroy et al. that enrolled 461 patients [35•]. It sought to compare 3-year disease-free survival (DFS) of chemotherapy followed by CRT and TME versus CRT followed by TME and adjuvant chemotherapy. The TNT group received 4 cycles of mFOLFIRINOX followed by 5 weeks of CRT with capecitabine then proceeded with TME. The CRT arm used capecitabine with 5 weeks of radiation and adjuvant use of either mFolfox6 or capecitabine based on center choice. Final results were presented at ASCO 2020 where compliance to CRT was not hampered by neoadjuvant chemotherapy. Rates of pCR (27.5% vs 11.7, $P < 0.001$) and 3-year DFS favored the experimental arm (75.7% vs 68.5%, HR 0.69, 95% CI 0.49–0.97, $P = 0.034$). 3-year OS was 90.8 vs 87.7% (HR 0.65, CI 0.40–1.05, $P = 0.077$).

The role of short-course radiotherapy followed by systemic chemotherapy has also been evaluated in the TNT setting given promising phase II data [36]. This led to the RAPIDO trial, a phase III trial comparing short course followed by 18 weeks of CAPOX/FOLFOX chemotherapy before surgery with standard of care CRT followed by surgery in 920 patients with locally advanced tumors (T4a-b or N2 or radiographic evidence of vascular invasion or mesorectal fascia or involved pelvic side wall nodes) and M0 disease. In the recently presented results, rates of pCR were 27.7% vs 13.8% (OR 2.40 [1.70–3.39]; $P < 0.001$) in the experimental and standard arms, respectively. At 3 years, disease-related treatment failure rate was 23.7% in the experimental arm and 30.4% in the standard arm (HR 0.76 [0.60–0.96]; $P = 0.02$). Distant metastasis and locoregional failure rates were 19.8% vs 26.6% (HR 0.69 [0.53–0.89]; $P = 0.004$) and 8.7% vs 6.0% (HR 1.45 [0.93–2.25]; $P = 0.10$), in the experimental and standard arms respectively. Overall health ($P = 0.192$), quality of life ($P = 0.125$) and low anterior resection syndrome score ($P = 0.136$) were comparable between the two treatment arms [37•].

There is also continued effort to evaluate novel sensitizers in the neoadjuvant setting. The NRG-GI002, a phase II trial by T.J. George et al., is investigating the role of immunotherapy PD-1 inhibitor pembrolizumab and the PARP inhibitor veliparib given in conjunction with CRT after mFOLFOX6 therapy. The primary outcome is the change in the neoadjuvant rectal cancer (NAR) score. This is an easier to measure surrogate marker for overall survival (OS) and DFS [13]. Secondary measure outcomes are 3-year OS and DFS, rate of pCR, and rate of sphincter preservation. Two arms of the study have completed accrual with results awaited, and in light of the previously presented data, the study may undergo a redesign.

De-Intensification of Therapy

Based on the previous section, it is quite certain that TNT, consolidation or induction chemotherapy with CRT, provides several benefits in the treatment of locally advanced rectal cancer. One of the known concerns of neoadjuvant CRT is the undesirable side effects of radiation. Long-term morbidities include greater than 5 bowel movements per day, rectal bleeding, bowel obstruction, and development of bowel necrosis/perforation/fistula [38]. Given advances in radiation, surgery, and chemotherapy, there is ongoing investigation looking into chemotherapy alone with selective addition of CRT versus CRT alone to treat patients with LARC prior to surgery. Perhaps patients could be spared the side effects of pelvic radiation. This is especially true for upper rectal cancer, where circumferential resection margin is not a major risk factor.

The phase III FOWARC trial, with its 3-arm trial design, included 495 patients with LARC randomly allocated to neoadjuvant CRT with 5FU leucovorin (de Gramont's regimen), neoadjuvant CRT with mFOLFOX6, or neoadjuvant chemotherapy (mFolFOX6) alone. Primary endpoint was 3-year DFS [39•]. There was no difference in the 3-year DFS (72.9%, 77.2%, and 73.5%, respectively $P = 0.71$) or the 3-year overall survival rate (91.3%, 89.1%, and 90.7% respectively, $P = .97$) between the arms. In this study, omitting radiotherapy did not lead to increase in rate of local recurrence in the chemotherapy alone arm. Exclusion of RT was associated with significantly less treatment-related toxicity and perioperative complications, while achieving comparable rates of recurrence-free and overall survival. The study provides only available prospective randomized data of relative benefit of chemotherapy alone in comparison with CRT.

In 2014, there was a single institutional pilot study from Memorial Sloan Kettering Cancer Center (MSK) that evaluated and treated 32 patients with stages II/III LARC using induction FOLFOX with selective use of CRT [11]. One hundred percent of the trial patients had R0 resections and 30 of 32 patients had tumor regression and went for TME without preoperative chemoradiotherapy. At 4 years, local recurrence was 0% and DFS was 84% indicating neoadjuvant chemotherapy followed by selective CRT did not adversely affect outcomes. These results warranted further investigation.

The PROSPECT trial (NCT01515787) is a multicenter phase II/III study looking to first ensure that neoadjuvant chemotherapy with 5FU and oxaliplatin followed by selective use of CRT in non-responders maintains a high rate of R0 resection and non-inferior for time to local recurrence (TLR). The phase III component directly compares neoadjuvant FOLFOX followed by selective CRT to standard neoadjuvant CRT. The trial has completed accrual but results are awaited. Similar to the PROSPECT trial, another study using the selective radiation approach is being conducted in China (FORTUNE, NCT02217020) but it uses FOLFOXIRI (5FU, leucovorin, oxaliplatin and Irinotecan) as the chemotherapy backbone. The primary endpoint for this study is the rate of tumor downstaging, and it has completed accrual but final results are pending.

TNT is beneficial as it gives the opportunity to assess chemosensitivity and tumor response prior to surgery and can help stratify patients needing surgery. In fact, several studies reporting a non-operative approach have suggested that patients who achieved a complete clinical response could be safely left with the rectum and have good long-term outcomes in localized rectal cancer [40–42]. To date, no prospective data is available comparing surgery or non-operative management; however, accumulating evidence reports favorable long-term outcomes with this approach. Majority of this evidence comes from the Brazilian institutional-level studies from Habr-Gama et al. where patients with stages I–III (>/=T2) rectal cancer who achieved a cCR after neoadjuvant CRT were allowed to skip surgery and follow a wait and watch (W&W) approach of intense local surveillance with good long-term outcomes. The inclusion of stage I tumors (up to 20% in initial study) limits application of the data. More recently, the International Watch & Wait Database published the outcomes of this strategy through a large-scale registry of pooled individual patient data from 1009 rectal cancer patients who did not undergo definitive surgery after neoadjuvant CRT [43]. All patients skipped definitive surgery and 889 patients (87%) had a cCR after neoadjuvant CRT. The 2-year cumulative incidence of local recurrence was 25·2% (95% CI 22.2–28.5%), most occurring within the first 2 years, and 97% of these were located in the bowel wall. Rate of distant failure (8%), 5-year OS (85%, 95% CI 80·9–87.7%), and 5-year disease-specific survival (94%, 95% CI 91–96%) was comparable to that seen with standard of care therapy.

Looking at prospective studies, the recently reported results of OPRA trial support this idea. In this trial, patients with stages II and III rectal adenocarcinoma were randomized to 4 months of FOLFOX or CAPOX before (induction) or after (consolidation) fluoropyrimidine-based CRT. Patients with complete or near-complete clinical response were offered watchful waiting and outcomes followed. The disease-free survival (primary endpoint) was comparable between induction and consolidation chemotherapy arms (78% vs 77%, $P = 0.90$) but the consolidation strategy was able to provide a 58% rate of organ preservation [44•]. The authors concluded that omitting surgery and adopting a wait and watch approach for patients that achieve a clinical complete response to TNT results in organ preservation without compromising survival in a high percentage of patients.

Despite the advances in the treatment of LARC to improve local control of disease, there has been a significant drive to establish treatment modalities to reduce incidence of distal recurrence as the 5-year distant relapse remains at around 30% [45–47].

Early-Stage Rectal Cancer

The role of tri-modality therapy for early-stage distal T1-2 N0 tumors to increase the rate of organ preservation is not well-established. For mid- and lower-third rectal cancers, the standard of care is total mesorectal excision (TME) done either by low anterior resection or by abdominoperineal resection with or without preoperative CRT. A proportion of these patients will require either a temporary or permanent stoma leading to an overall diminished quality of life [48]. More than half of patients will go on to experience a degree of fecal incontinence and may also have autonomic nerve damage leading to either urinary continence or retention (25–34%) and sexual dysfunction [49]. This leads to concerns that radical surgery—which evolved to treat locally advanced and symptomatic tumors—may not be the optimal method of treatment for early-stage tumors.

Early rectal tumors may be locally excised either by local excision (LE) or by transanal endoscopic microsurgery (TEMS). These procedures seek to omit TME and preserve the rectum. However, this increases the risk of residual microscopic lymph node metastasis leading to local failure. Prior studies have explored the use of pelvic chemoradiation followed by transanal microsurgery as a means to increase organ preservation but have shown high complication rates with LE and TEMS after CRT including 30-day readmissions, wound dehiscence, grades 3–4 complications, and adverse effects on bowel, sexual, and urinary function [49, 50]. Also, patients who develop recurrence following this strategy are difficult to salvage as re-irradiation is not usually an option. The role of chemotherapy to downstage tumor and address micrometastatic

disease in early-stage disease has not been explored much. Given the significant advances in combination chemotherapy, investigators have hypothesized that the use of combination chemotherapy in the neoadjuvant setting will help downsize primary low rectal tumors leading to improved local excision rates and reduce the number of patients that need radical surgery and not compromise oncologic outcomes.

The Canadian Cancer Trials Group is investigating the effects of upfront neoadjuvant chemotherapy with either FOLFOX or CAPOX in early-stage rectal cancer prior to tumor excision. The NEO: Neoadjuvant Chemotherapy, Excision and Observation for Early Rectal Cancer (NCT03259035) is a single-arm phase II trial that is two-staged with the primary endpoint of organ (rectum) preservation rate of 65%. Neoadjuvant regimen selection is either six 2-week cycles of FOLFOX or four 3-week cycles of CAPOX prior to surgery. Secondary outcomes include 3-year measurements of locoregional recurrence, distant relapse rate, DFS, and rate of postoperative complications. This trial has completed accrual, and final results are awaited (CO.28-NCT03259035). Another ongoing trial, GI-116: Phase II Study of Organ Preservation in Early Rectal Cancer Patients (NCT03548961), is a single-arm phase II study investigating neoadjuvant combination chemotherapy followed by local excision and postoperative chemoradiotherapy in patients with early-stage, low rectal adenocarcinoma. The primary endpoint is the number of patients whose tumor can be resected by local excision with negative margins. Eligible patients will undergo 12 weeks of FOLFOX followed by restaging of the primary tumor with pelvic MRI and/or sigmoidoscopy 2–4 weeks after completing therapy. Those who respond will proceed with local excision 6–12 weeks after completing neoadjuvant chemotherapy and 4–12 weeks after local excision will undergo 5-FU-based chemoradiotherapy.

Conclusions

There have been substantial advances in treatment of rectal cancers in the last 20 years. The role of neoadjuvant chemotherapy continues to advance in the setting of early-stage and locally advanced rectal cancers. In a disease process where the pathologic stage at the time of surgery is the best predictor of DFS, there is strong incentive to improve upon optimal delivery of systemic therapy prior to surgical resection. The current standard of care for LARC remains either neoadjuvant CRT followed by surgery and adjuvant chemotherapy or TNT; however, these regimens have not been compared prospectively. There remains a lack of evidence of the effectiveness of novel sensitizing agents in LARC. Table 1 provides a summary of ongoing or recently completed studies in this area. The NRG-GI002 phase II trial is investigating the role of immunotherapy PD-1 inhibitor pembrolizumab and the

Table 1 Ongoing phase II/III clinical trials evaluating neoadjuvant therapy for rectal cancer

Trial	Phase	Experiment arm	Comparator arm	Primary endpoint	Secondary outcomes
NCT01308190 Tau TEM	III	Capecitabine + radiotherapy -> transanal endoscopic microsurgery	Standard TME	2-Year local recurrence	
NCT02945566 STAR-TREC	II	Long-course concurrent chemoradiation (arm 1) or short-course radiotherapy (arm 2)	Standard TME	Feasibility trial	Full listing on clinicaltrials.gov
NCT02921256 NRG-GI002	II	mFOLFOX6 -> CRT + pembrolizumab (arm 2) or veliparib (arm 3)	Neoadjuvant mFOLFOX6 -> CRT (arm1)	3-Year change in NAR score	3-Year OS, DFS, rate of pCR
NCT01515787 PROSPECT	II/III	FOLFOX -> ± CRT -> surgery -> FOLFOX or CRT -> chemo	CRT - > surgery - > FOLFOX	8-Year R0 rate, DFS, time to local recurrence	8-Year pCR, OS, adverse event profiles, of pre- versus postoperative CRT
NCT03548961 GI-116 (Early-stage low rectal cancer)	II	FOLFOX -> local excision -> CRT		Rate of local excision with negative margins	5-year OS, DFS Rate of improved bowel function/sexual function/health related QOL
NCT02977052 NEO (early-stage rectal cancer)	II	FOLFOX or CAPOX followed by surgery		Rate of organ preservation	3-Year local regional relapse rate, distant relapse rate, DFS, rate of postoperative complication

PARP inhibitor veliparib given in conjunction with CRT after mFOLFOX6 therapy. In regard to early-stage low rectal cancers, the GI-116 and NEO phase II clinical trials will assess the role of neoadjuvant combination chemotherapy leading increased rates of less invasive surgery that spares the rectum.

Compliance with Ethical Standards

Conflict of Interest Namrata Vijayvergia has received consultancy fees from Lexicon, Novartis, HalioDx, and Sun Pharma and grants from Merck and Bayer. Thomas Holden declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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