Current Colorectal Cancer Reports (2020) 16:39–48
https://doi.org/10.1007/s11888-020-00451-6

RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (PP LEE AND AC RALDOW, SECTION EDITORS)

The Evolving Landscape of Neoadjuvant Radiation Therapy for Locally Advanced Rectal Cancer

Stephanie M. Yoon[1] · Percy Lee[2] · Ann Raldow[1]

Published online: 27 April 2020

Abstract

Purpose of Review Neoadjuvant long-course chemoradiation (LCRT) and short-course radiotherapy (SCRT) are evidence-based treatment options for locally advanced rectal cancer. Both paradigms improve local control but have not shown to impact distant metastases or overall survival. Herein, we compare these two radiation approaches and review their role in the multidisciplinary management for locally advanced rectal cancer.

Recent Findings There are no significant differences in disease outcomes between LCRT and SCRT. Delaying surgery after either radiation regimens is safe and leads to tumor downstaging without compromising oncologic outcomes. Attempts to incorporate chemotherapy to intensify neoadjuvant radiation regimens are under active investigation.

Summary LCRT and SCRT are proven neoadjuvant regimens that improve local control. Supporters of LCRT emphasize the higher likelihood for tumor downstaging and sphincter preservation, while those favoring SCRT highlight lower acute toxicities, decreased costs, and patient convenience. Delaying surgery after either LCRT or SCRT is safe and provides pathologic downstaging. The optimal timing of surgery has yet to be determined. There is growing interest in total neoadjuvant therapy which incorporates chemotherapy with neoadjuvant radiation.

Keywords Neoadjuvant · Short course · Long course · Radiation · Chemoradiation · Rectal cancer

Introduction

Colorectal cancer is the third most common cancer in the United States (USA) in both men and women. In 2019, it is expected that there will be 44,180 new cases of and 51,020 deaths from rectal cancer [1]. Oftentimes, patients present with locally advanced, deeply invasive (T3–4), or node-positive tumors require a multimodality treatment approach to achieve optimal outcomes. For locally advanced rectal cancer, NCCN guidelines recommend neoadjuvant chemoradiation followed by total mesorectal excision (TME) and adjuvant chemotherapy. Radiation delivered prior to TME has consistently shown to reduce local and regional pelvic recurrences. Two standard neoadjuvant radiation paradigms are long-course chemoradiation (LCRT) (50.4 Gy in 28 fractions given concurrently with fluorouracil-based chemotherapy) and short-course radiotherapy (SCRT) (25 Gy in 5 daily fractions) [2].

The role for neoadjuvant LCRT was established by the French FFCD 9203 and German Rectal Cancer trials [3–5]. The French FFCD 9203 trial demonstrated that patients receiving pre-operative chemoradiation had significantly lower 5-year local recurrence (LR) rates (8.1%) compared to patients receiving radiation therapy alone (16.5%, $p < 0.05$), though without improvements in 5-year overall survival (OS) or sphincter preservation. The trial randomized 733 T3–4 rectal cancer patients to either pre-operative radiotherapy alone (45 Gy in 25 daily fractions) or radiotherapy given concurrently with 5-FU and leucovorin followed by non-TME surgery 3 to 10 weeks later. The German Rectal Cancer trial similarly found fewer local relapses with neoadjuvant LCRT followed by TME compared to TME followed by adjuvant

The editors would like to thank Dr. Jeffrey Meyer for taking the time to review this manuscript.

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer.*

✉ Ann Raldow
araldow@mednet.ucla.edu

[1] Department of Radiation Oncology, University of California Los Angeles, 200 Medical Plaza Driveway, Suite B265, Los Angeles, CA 90095, USA

[2] Department of Radiation Oncology, MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

LCRT. Patients with T3–4 or node-positive rectal cancer were randomized to either pre-operative or post-operative chemoradiation with 50.4 Gy in 28 fractions to the tumor and pelvic lymph nodes given concurrently with continuous infusion of 5-FU. The 10-year incidences of distant metastases (DMs), disease-free survival (DFS), and OS were not different between study groups. Acute and late treatment-related morbidity were reduced with neoadjuvant LCRT.

In parallel, a shorter course of pre-operative radiation also effectively reduced local recurrence rates over surgery alone. The Swedish Rectal Cancer Trial demonstrated that patients undergoing SCRT with 25 Gy over 5 daily fractions followed by surgery within 1 week had lower rates of LR (11% vs. 27%, $p < 0.001$), improved 5-year OS (58% vs. 48%, $p = 0.004$), and 9-year cause-specific survival (CSS) (74% vs. 64%, $p = 0.002$) compared to those undergoing surgery alone [6]. These findings remained significant after median follow-up of 13 years [7]. Of note, patients in this trial did not undergo TME, which is considered standard of care today. The poorer outcomes among patients undergoing surgery alone were thought to be from inferior surgical techniques.

To specifically address the value of pre-operative SCRT in the setting of TME, the Dutch trial randomized 1861 patients with resectable rectal cancer to either SCRT followed by TME or TME alone [8]. Patients with SCRT had significantly lower 10-year LR rates but no improvement in OS. On subset analysis, TNM stage III rectal cancer patients with negative circumferential resection margins (CRMs) who underwent SCRT had improved 10-year OS (50%) compared to those undergoing surgery alone (40%, $p = 0.032$) [9].

Despite evidence for the effectiveness of SCRT, LCRT remains standard of care in the USA; however, SCRT is utilized more in countries outside the USA and in academic centers. In this review, we summarize the clinical trials comparing LCRT and SCRT, as well as potential reasons for why clinicians may favor one regimen over the other. We also discuss trials investigating the optimal timing of surgery after neoadjuvant radiation and intensification of neoadjuvant radiation with chemotherapy, or total neoadjuvant therapy (TNT), to improve oncologic outcomes.

Comparison of Oncologic Outcomes Between Neoadjuvant Long-Course Chemoradiation and Short-Course Radiation

To date, two prospective randomized trials comparing LCRT to SCRT for locally advanced rectal cancer have shown no major differences in oncologic outcomes. Findings are summarized in Table 1.

The Polish trial randomized 316 patients from 19 institutions between 1999 and 2002 with palpable T3–4 rectal adenocarcinomas to 25 Gy in 5 fractions or 50.4 Gy in 28 fractions with bolus 5-FU and leucovorin [11, 12]. Patients were staged with digital rectal exams (DREs), endorectal ultrasound, and pelvic CT scans. Patients with distant disease were excluded based on results of chest X-ray and/or CT of the abdomen. TME followed within 1 week of SCRT or 4–6 weeks after LCRT, and post-operative chemotherapy was optional. There were higher pathologic complete response (pCR) rates after LCRT (16.1% vs. 0.7%, $p < 0.001$), and lower rates of positive radial margins (4% vs. 13%, $p = 0.017$). Despite significant tumor downstaging, no differences in sphincter preservation rates (61% vs. 58%, respectively; $p = 0.57$) were observed. Long-term results showed no significant differences in LR rates, 4-year OS, or DFS between the two regimens [11]. While LCRT was associated with higher acute toxicity (18.2% vs. 3.2%, $p < 0.001$), severe late toxicity, defined as grade ≥ 3 or requiring major surgical intervention or hospitalization, was not significantly different between the two neoadjuvant regimens (10.1% vs. 7.1%, $p = 0.36$). Of note, 39.5% of patients in the SCRT group had pT1–2 disease, thought to result from either tumor downstaging when surgery was delayed beyond 10 days (which occurred in 12.7% of patients) or from inaccurate clinical staging.

More recently, the TROG 01.04 study compared SCRT followed by surgery within 1 week to LCRT followed by surgery within 4–6 weeks. Patients with cT3 and N0–2 rectal adenocarcinoma located within 12 cm from anal verge were included [13]. After median follow-up of 5.9 years, there was significantly more tumor downstaging with LCRT (45% vs. 28%, $p = 0.002$) and increased pCR rates (15% vs. 1%, $p < 0.001$). Similar to the Polish study, these findings did not translate to reduced rates of anterior peritoneal resections (APRs) for distal tumors (79% vs. 77%, $p = 0.87$), 3-year LR (7.5% vs. 4.4%, $p = 0.24$), 5-year distant recurrence rates (27% vs. 30%, $p = 0.92$), or improvement in 5-year OS (74% vs. 70%, $p = 0.62$). Late toxicity was not significantly different between the two arms (5.8% vs. 8.2%, $p = 0.53$). A subset analysis of patients with distal tumors < 5 cm from anal verge ($n = 79$) showed a cumulative LR incidence of 12.5% vs. 0% after SCRT and LCRT, respectively ($p = 0.26$). Although this cumulative LR incidence was not statistically significant, the trial did not have sufficient power to detect a true difference in this subgroup. Additionally, possible reasons why higher pathologic downstaging with neoadjuvant LCRT did not lead to higher sphincter preservation rates could be that the extent of tumor downstaging was not sufficient enough to alter surgical approach or that surgeons made surgical decisions based on presenting clinical characteristics. SCRT was not expected to reduce APR rates due to insufficient time for tumor downstaging.

There are some notable differences between the TROG and Polish trials. The TROG trial assessed patients with endorectal ultrasound or pelvic MRI, with sigmoidoscopy and biopsy, compared to DRE and pelvic CT scans in the Polish trial. Additionally, patients in the TROG trial were treated with

Table 1 Key trials summarizing oncologic outcomes and toxicities from LCRT and SCRT

Study	Description	Year	Inclusion criteria	Patients	Dose and fractionation	TME	Timing of surgery	%LAR	%APR	Local Recurrence	Overall Survival	pCR	Acute G3–4 toxicity	Late G3–4 toxicity
German Rectal Cancer Trial [4, 5]	Pre-op vs. Post-op LCRT	2004	T3–4N+, M0 Age < 75, < 16 cm from anal verge,	799	50.4 Gy/28fxns + continuous 5-FU (1000 mg/m^2)	Yes	4–6 weeks	69.0% vs. 71.0%	26.0% vs. 23.0%	(5-year) 6.0% vs. 13.0%* (10-year) 7.1% vs. 10.1%*	(5-year) 76.0% vs. 74.0% (10-year) 59.6% vs. 59.9%	8.0% vs. 0%*	27.0% vs. 40.0%*	14.0% vs. 24.0%*
French FFCD 9203 [3]	Pre-op RT vs. LCRT	2006	T3–4N0–2, M0 Age < 75	733	45 Gy/25fxns ± concurrent 5-FU (350 mg/m^2/day) + leucovorin	No	3–10 weeks	54.4% vs. 52.4%	41.7% vs. 42.3%	(5-year) 16.5% vs. 8.1% *	(5-year) 67.9% vs. 67.4%	3.6% vs. 11.4%*	2.7% vs. 14.6%*	–
Swedish Rectal Cancer Trial [6, 7]	Pre-op SCRT vs. surgery alone	1997	Resectable, M0 Age < 80, tumor below sacral promontory,	1168	25 Gy/5 fxn	No	1 week	–	–	(5-year) 11% vs. 27%* (13-year) 9% vs. 26%*	(5-year) 58% vs. 48%* (13-year) 38% vs. 30%*	–	–	–
Dutch TME Trial [8–10]	Pre-op SCRT vs. surgery alone	2001	Resectable, M0 < 15 cm from anal verge	1861	25 Gy/5 fxn	Yes	1 week	65.0% vs. 67.0%	28.0% vs. 26.0%	(2-year) 2.4% vs. 8.2%* (10-year) 5.0% vs. 11.0%	(2-year) 82.0% vs. 81.8% (10-year) 50.0% vs. 40.0%	–	–	56.0% vs. 35.0%*
Polish Trial [11, 12]	Pre-op SCRT vs. LCRT	2004	T3–4 Palpable on DRE	316	25 Gy/5fxns 50.4 Gy/28fxns + bolus 5-FU (325 mg/m^2/day) and leucovorin (20 mg/m^2)	Yes	1 week 4–6 weeks	61.0% vs. 58.0%	32.0% vs. 36.0%	(4-year) 9.0% vs. 14.2%*	(4-year) 67.2% vs. 66.2%	0.7% vs. 16.1%*	3% vs. 18%*	7.1% vs. 10.1%
TROG 01.04 [13, 14]	Pre-op SCRT vs. LCRT	2012	T3N0–2 M0 < 12 cm from anal verge	326	25 Gy/5fxns 50.4 Gy/28fxns + continuous 5-FU (225 mg/m^2/day) and leucovorin (20 mg/m^2)	Yes	1 week 4–6 weeks	63.0% vs. 69.0%	37.0% vs. 31.0%	(3-year) 7.5% vs. 4.4%	(5-year) 74.0% vs. 70.0%	1% vs. 15%*	0% vs. 5.6% (RT dermatitis); 3.7% proctitis; 14.2% diarrhea; 3.1% nausea	5.8% vs. 8.2%
Stockholm III [15••, 16, 17]	SCRT immediate surgery vs. SCRT delay surgery vs. LCRT	2017	Resectable, M0 < 15 cm from anal verge	840	25 Gy/5fxns 50/25fxns	Yes	1 week (immediate SCRT) 4–8 weeks (delay SCRT and LCRT)	61.0% vs. 53.0% vs. 72.0%	36.0% vs. 41.0% vs. 19.0%	2.2% vs. 2.8% vs. 5.4%	(5-year) 73.0% vs. 76.0% vs. 78.0%	0.3% vs. 10.4% vs. 2.2%	0% vs. 7.0% vs. 5.0%	–

LCRT long-course chemoradiation, *SCRT* short-course radiation, *TME* total mesorectal excision, *LAR* low anterior resection, *APR* abdominal peritoneal resection, *pCR* pathologic complete response, *G3–4* grade 3 to 4

*Statistically significant

continuous infusion (as opposed to bolus) 5-FU. Several studies have reported superior outcomes with continuous infusion 5-FU with respect to pCR rates, time to relapse, and survival [18, 19]. Finally, both arms in the TROG trial received four cycles of adjuvant chemotherapy, while the adjuvant chemotherapy was optional and variably administered in the Polish trial.

Given the results of these studies, the optimal fractionation and timing of surgery after radiation remains controversial. The Stockholm III trial aimed to compare three different schedules of radiotherapy [15••]. This non-inferiority trial randomized patients with resectable tumors located within 15 cm from the anal verge to SCRT followed by immediate surgery 1 week later, SCRT with delayed surgery 4–8 weeks later, and long-course radiation with delayed surgery by 4–8 weeks. There were no significant differences in time to LR among the three groups (33.4 vs. 19.3 vs. 33.3 months, respectively). The cumulative incidence of LR (2.2% vs 2.8% vs. 5.4%), 5-year OS (73% vs. 76% vs. 78%), and acute toxicities (< 1% vs. 7% vs. 5%) were similar among all three groups. The two SCRT groups were considered non-inferior to long-course radiation. Comparing between the two SCRT regimens, the overall risk for post-operative complications was significantly lower when surgery was delayed, though the frequency of severe complications requiring reoperation was no different. Lower risk for any post-operative complications from SCRT and delayed surgery was partially offset by 7% of patients experiencing grade 3 toxicity requiring hospital admission.

A planned interim analysis of the Stockholm III trial compared pathologic outcomes between the two SCRT groups and was published in 2015. There was a higher rate of pCR (11.8% vs. 1.7%) and Dworak grade 4 tumor regression (10% vs. 1.7%) with SCRT and delayed surgery compared to SCRT with immediate surgery [20]. In 2019, tumor regression outcomes were reported for all three study groups [21•]. After median follow-up of 5.7 years, pCR from SCRT and delayed surgery remained higher (10.4%) than pCR rates achieved from SCRT and immediate surgery (0.3%) and long-course radiation with delayed surgery (2.2%). Furthermore, achieving a pCR was significantly associated with improved time to recurrence (HR = 0.27) and OS (HR = 0.51, $p = 0.046$). Despite differences in pCR rates among neoadjuvant regimens, there were no significant impacts to local control, distant metastasis, or OS, consistent with prior reports. Interestingly, patients achieving near-complete response (consistent with Dworak grade 3 tumor regression) had worse disease control or survival compared to patients with true pCR.

The Stockholm III trial is the first to report a higher pCR rate with SCRT and delayed surgery over long-course radiation. Until now, most retrospective and prospective series have reported superior pCR rates with LCRT over either SCRT regimens (immediate or delayed surgery) [13, 16, 17, 22–24]. About half the patients in the Stockholm III trial had pre-operative staging and clinical information available, making generalizability and interpretation of the data difficult. Additionally, this study did not evaluate lymph node regression, which has also been associated with improved oncologic outcomes [25, 26]. There has been conflicting evidence in the literature as to whether patients must achieve a pCR to benefit from a lower risk of disease recurrence, or whether any degree of tumor downstaging is beneficial [27, 28]. Many high-quality reports suggest that pCR may not be a good surrogate for oncologic outcomes like OS, since it does not take into account potential micrometastatic disease [29].

There are other limitations with this trial. Due to limited hospital resources in some participating centers and concerns for the long delay to surgery with long-course radiation, the trial was amended 1 year after opening. Randomization was subsequently limited to the two SCRT arms yet analyzed with intention-to-treat, which may not take into account for potential imbalances among the study groups. Additionally, the Stockholm trial did not give concurrent chemotherapy in the long-course radiation arm. Studies have since shown that concurrent chemotherapy with long-course radiation improves local control [3, 30, 31]. Finally, acute toxicities arising from SCRT and immediate surgery may be confused for early post-operative complications [32]. This trial suggested that delaying surgery after SCRT by 4–8 weeks is safe and yields similar oncologic outcomes as SCRT with immediate surgery.

Stockholm III highlights the importance of further exploring the optimal timing of surgery following neoadjuvant therapies for certain subsets of patients. The benefits of delaying surgery without impacting oncologic outcomes have led some investigators to evaluate the idea of intensifying neoadjuvant radiotherapy with additional chemotherapy to improve oncologic outcomes.

Optimal Timing of Surgery Following Neoadjuvant Therapy

The optimal timing of surgery after radiation has yet to be determined. GRECCAR-6 found that delaying surgery beyond 11 weeks after neoadjuvant LCRT led to poorer-quality TMEs and increased surgical morbidity [33]. This phase III multicenter trial recruited patients with cT3–4 and/or node-positive tumors located in the mid or distal rectum. All patients received 45–50 Gy with concurrent 5-FU or capecitabine and were then randomized to surgery 7 or 11 weeks later. Morbidity was significantly worse when surgery was prolonged by 11 weeks (32% vs. 44.5%, $p = 0.040$). These patients experienced more medical complications (19.2% vs. 32.8%, $p = 0.0137$) and worse-quality TMEs, in which the mesorectum was not completely resected (90% vs. 78.7%, $p = 0.0156$).

The recent Stockholm III trial suggests that delaying surgery after SCRT by 4–8 weeks provides an opportunity to improve tumor downstaging while not impacting OS or recurrence rates [21•, 34, 35]. In addition, a retrospective study suggests that the optimal timing for resection is within 7 to 10 weeks following LCRT [35]. In this study, downstaging rates peaked between 6 and 7 weeks; ypCR rates increased up to 6 weeks after surgery but declined beyond 10 weeks.

Quality of Life, Cost-Effectiveness, and Utilization of Neoadjuvant Short- and Long-Course Regimens

As the optimal neoadjuvant regimen is still debated, recent reports have assessed toxicity and cost-effectiveness to guide clinicians in deciding between LCRT and SCRT prior to immediate surgery.

Acute toxicities and post-operative complications from TROG 01.04 were reported by Ansari et al. [14]. All patients randomized to SCRT were able to complete the treatment course, and 93% of patients completed LCRT. A significantly higher proportion of patients experienced at least one acute toxicity with LCRT (99.4%) compared to SCRT (72.3%) ($p < 0.001$). More specifically, about 3–5% of patients after LCRT experienced significant grade 3 or higher radiation dermatitis, proctitis, nausea, fatigue, and/or diarrhea. However, there were no significant differences in surgical complication rates between the two neoadjuvant regimens. There was a trend towards more permanent stomas (38% vs. 29.8%, $p = 0.13$) and anastomotic breakdowns (7.1% vs. 3.5%, $p = 0.26$) for patients undergoing SCRT. A trend towards more perineal wound complications was observed in patients undergoing LCRT (38.3% vs. 50%, $p = 0.26$).

There are more limited data reporting long-term toxicities following SCRT, but most studies generally report that quality of life (QOL) is similar between LCRT and SCRT at least 1 year after completing neoadjuvant therapy. Compared to patients undergoing SCRT, patients who had LCRT experienced a greater decline in emotional, physical, cognitive, and social functioning 3–6 months after neoadjuvant therapy. These QOL domains improved with time, and eventually became comparable to patients after SCRT after 1–2 years [10, 36, 37]. One study reported a higher degree of bowel function 14 years following SCRT and TME compared to TME alone among patients enrolled on the Dutch TME trial from 1996 to 1999 [8, 38]. In the long-term toxicity analysis, 583 of the original 1530 patients enrolled on the Dutch TME trial were alive at time of this study and were given a set of questionnaires assessing low anterior resection syndrome (LARS) and QOL [38]. LARS is a constellation of symptoms that include fecal incontinence, bowel urgency, frequent or fragmented bowel movements, bloating, or sensation of incomplete bowel evacuation. Forty-six percent of study patients experienced "major LARS," 22% experienced "minor LARS," and 32% with "no LARS." Fifty-six percent of patients with major LARS underwent SCRT and 35% had TME alone. On multivariate analysis, patients undergoing SCRT and age less than 75 years were at high risk of developing major LARS. When stratified by the degree of LARS experienced by patients, those with major LARS had significantly worse QOL outcomes compared to other subgroups. Finally, regardless of neoadjuvant regimen, 44–60% of patients with LAR tend to experience major bowel dysfunction, while patients who had APR have more urinary and sexual dysfunction [37, 39, 40].

A recent cost-effectiveness analysis comparing SCRT followed by immediate surgery and LCRT followed by delayed surgery concluded that SCRT was more cost-effective for most locally advanced rectal cancer patients [41]. This study included sensitivity analyses varying costs of surgery and radiation over a reasonable range, and SCRT still remained the higher value treatment. However, LCRT was the cost-effective approach for distally located tumors assuming a higher proportion of patients undergoing LCRT would have sufficient downstaging to undergo a sphincter-sparing surgery compared to patients having undergone SCRT. The cost-effectiveness of SCRT versus LCRT was dependent on the utilities of the disease-free states after APR and LAR, highlighting the importance of preference sensitive care.

Despite evidence reporting equivalent oncologic outcomes and long-term toxicities between SCRT with immediate surgery and LCRT, SCRT is still under-utilized, especially in the USA. A survey of American radiation oncologists who regularly treat patients with rectal cancer showed that 96% of respondents preferred LCRT, and 44% had never recommended SCRT [42]. Some reasons why clinicians may offer SCRT include less acute toxicity, patient convenience, and lower costs [42–44]. SCRT was usually not recommended due to insufficient tumor downstaging for potential sphincter preservation and desire for long-term follow-up [42]. In light of the Stockholm III trial and as US healthcare moves towards a more capitated payment model, SCRT may be utilized more often in the future.

Intensifying Neoadjuvant Radiation with Chemotherapy

Local failure rates with neoadjuvant radiation followed by TME are low (5–10%) [3, 5, 9]. However, rectal cancer patients often fail distantly, which may explain the lack of OS benefit from radiation.

Intensifying neoadjuvant radiation with concurrent multidrug chemotherapy has been evaluated in several phase II–III randomized trials. At least 5 clinical trials have incorporated oxaliplatin with 5-FU or capecitabine during LCRT. None have shown improvement in pCR rates or OS [45–49]. Only the German CAO/ARO/AIO-04 trial demonstrated better DFS with neoadjuvant LCRT with 5-FU and oxaliplatin

(75.9% vs. 71.2%, $p = 0.03$) [46]. Early phase trials have also evaluated incorporating other agents (irinotecan, cetuximab, bevacizumab, and tyrosine kinase inhibitors) with 5-FU-based chemoradiation, but have had variable results [50–55].

Limited trials have studied concurrent chemotherapy with SCRT due to concerns for worsening acute toxicities. A series of trials from South Korea evaluated the safety and feasibility of concurrent chemotherapy with SCRT. Outcomes were dependent on the chemotherapy agent used. One of the phase 2 trials included patients receiving SCRT with concurrent bolus injections of 5-FU and leucovorin, which led to severe grade 3 or higher acute toxicities in 38% of patients and poor pathologic responses compared to conventional LCRT [56]. However, continuous infusion of 5-FU or oral capecitabine concurrently with SCRT led to better toxicity profiles and comparable pathologic outcomes to LCRT [57, 58].

In an attempt to minimize acute toxicities, early phase trials demonstrated the feasibility of hyperfractionated SCRT [59, 60]. Delivering a BED > 30 Gy was associated with improved local control and reduced mortality rates, compared to regimens with ≤ 30 Gy. A Japanese study also gave capecitabine concurrently with hyperfractionated SCRT (25 Gy in 2.5 Gy per fraction given twice daily) for T3Nx low rectal cancer patients [61]. While 31% of patients experienced grade 1 cystitis and 5% experienced grade 2 diarrhea, there were no grade 3 or higher acute toxicities. Short-term oncologic outcomes appeared favorable, with 76% of patients experiencing tumor downstaging and 10% achieving pCR. Two-year local relapse-free survival was 95% and 2-year recurrence-free survival was 91%. Overall, hyperfractionated SCRT with or without concurrent chemotherapy is a feasible and promising alternative to standard SCRT and LCRT.

Interest in chemotherapy prior to or soon after neoadjuvant radiation is growing as well. This approach has been termed total neoadjuvant therapy (TNT). Studies from the UK reported high radiographic response rates with induction capecitabine and oxaliplatin (CAPOX) prior to initiating neoadjuvant LCRT [62, 63]. In their most recent report, 74% of patients were found to have radiographic response rates after induction chemotherapy, 89% achieved radiographic responses after LCRT, and 20% had pCR. Three-year relapse-free survival (RFS) and OS were high at 74% and 83%, respectively. The GCR-3 phase II trial showed similar pCR rates of 14.3% after induction CAPOX. This trial compared induction versus adjuvant CAPOX to LCRT and surgery. pCR rates, distant failure rates, and OS were similar between the two arms, but patients were found to have better compliance and toxicity profiles with induction CAPOX [64]. NRG-G1002 (NCT02921256) is an ongoing phase II randomized trial with induction FOLFOX and LCRT as the control arm. There are multiple experimental arms involving induction FOLFOX and LCRT with concurrent 5-FU and targeted agents like veliparib or pembrolizumab before TME.

The UK COPERNICUS trial assessed induction CAPOX with SCRT and immediate surgery specifically among rectal cancer patients who had T3–4 on MRI with either extra-mural venous invasion or lymph node involvement. Post-induction chemotherapy MRI showed 73% tumor response rate, and 37% of patients having tumor regression grade (mrTRG) of 1–2. Delaying time to surgery with induction chemotherapy did not jeopardize surgical outcomes, and 74% of patients had high-quality surgeries [65].

Neoadjuvant chemotherapy given after radiation but before surgery is another total neoadjuvant therapy strategy under active investigation. Most studies have administered consolidation chemotherapy after SCRT. Several phase II trials have employed consolidation CAPOX after SCRT, resulting in high pCR rates ranging from 25 to 30% [66, 67]. Among locally advanced T3–4 or node-positive tumors, 3-year local control and OS were 94% and 65%, respectively [66]. One trial assessed the efficacy of SCRT and consolidation CAPOX with bevacizumab among high-risk patients with limited resectable metastases. This treatment regimen achieved relatively long-term survival for this subset of patients despite high distant recurrence rates (80.6%). After median follow-up of 8 years, OS was 32% and DFS was 28% [67]. Similar favorable outcomes using consolidation FOLFOX (4 cycles) after SCRT among rectal cancer patients (T3–4, any N and M) planned for resection of primary tumor were reported [68–70]. At time of surgery, ~ 70% of patients had tumor downstaging. Twenty-five to 28% of patients had pCR, though 32% still had node-positive disease. Local control after 30 months of follow-up was 95%, and 87% of patients were free from distant metastases [68]. More recently, a single institution reported their experience with 26 patients with locally advanced rectal adenocarcinoma who underwent SCRT followed by mFOLFOX6 or CAPOX prior surgery [70]. Of 19 patients who underwent post-neoadjuvant treatment endoscopic evaluation, 9 patients (47%) were noted to have complete clinical response. Twenty (20) patients ultimately underwent surgery, of which 35% were observed to have pathologic complete response. Twenty-seven percent (27%) of patients experienced CTCAE grade 2 radiation-associated proctitis and 30% experienced Clavien-Dindo grade 3 postoperative complications within 30 days of surgery.

Early comparisons between patients undergoing SCRT and consolidation FOLFOX with those who had standard LCRT have been made [71, 72]. R0 resection and pCR rates from TNT are comparable to those after LCRT. R0 resection rates from TNT have been ~ 77% and pCR rates range from 16 to 28% [72]. Results have been mixed regarding the impact of TNT on disease recurrence and OS [71, 72]. The STELLAR trial is a multicenter phase III trial from China that compared SCRT and 4 cycles of consolidation CAPOX to LCRT with capecitabine. TME followed 6–8 weeks later in both groups, and additional two to six courses of CAPOX post-operatively

were prescribed for both groups [73]. While there were similar R0 resection rates between the two groups (92.9% vs. 89.5%, $p = 0.593$), a significantly higher proportion of patients who were randomized to SCRT and CAPOX achieved pCR rates compared to patients randomized to receive LCRT (26.2% vs. 5.3%, $p = 0.011$). Moreover, a significantly higher proportion of patients receiving SCRT and CAPOX were able to complete all planned treatments compared to LCRT (76.5% vs. 49%, $p = 0.000$). The RAPIDO is another randomized trial comparing oncologic outcomes after SCRT and 6 cycles of consolidation CAPOX before TME, and standard LCRT. The RAPIDO trial recently completed, and results are anticipated.

Replacing Neoadjuvant Radiation with Chemotherapy

The possibility of omitting neoadjuvant radiation entirely is being explored. Approximately 30% of patients eventually develop distant metastases, and efforts focusing on neoadjuvant chemotherapy alone without radiation to address this issue are underway.

The Chinese FOWARC trial is a phase III trial that randomized 495 cT1-4N1-2 rectal cancer patients to one of three arms: standard LCRT with 5-FU and 7 cycles of adjuvant 5-FU, LCRT with FOLFOX6 and adjuvant FOLFOX6, or perioperative mFOLFOX6 alone [74]. Initial results reported that perioperative mFOLFOX6 alone led to worse pCR rates (14% vs. 27.5% vs. 6.6% respectively), tumor downstaging (37.1% vs. 56.4% vs. 35.5%), and nodal downstaging (80.1%, 87.4%, 73.5%) compared to the other two study groups involving LCRT. Toxicities from perioperative mFOLFOX6 group were not reported, but using FOLFOX concurrently with LCRT led to high-grade 3–4 GI toxicities Despite these initial results, no significant differences in primary endpoint (3-year DFS) (72.9% vs. 77.2% vs, 73.5%, $p = 0.709$), local recurrence after R0/1 resections (8% vs. 7% vs. 8.3%, $p = 0.873$), or 3-year OS (91.3% vs. 89.1% vs. 90.7%, $p = 0.971$) were observed [75]. Thus, this study calls for further investigation into the utility of radiation in neoadjuvant regimens for locally advanced rectal cancer.

The results of the ongoing Alliance PROSPECT trial (NCT01515787) are pending and will be informative. This phase II–III trial is randomizing cT2-3N0-1 patients to either LCRT with 5-FU or capecitabine or to neoadjuvant FOLFOX for 6 cycles alone. LCRT will be selectively provided to patients in the neoadjuvant FOLFOX group whose tumor does not decrease by > 20% after completing neoadjuvant therapy.

Conclusion

Neoadjuvant radiotherapy with either LCRT or SCRT prior to TME yields low rates of pelvic recurrences. Recent prospective randomized trials comparing LCRT to SCRT suggest no differences in oncologic outcomes or toxicity. Compared to SCRT followed by immediate surgery, LCRT followed by delayed TME has been associated with higher likelihood for tumor downstaging. While delaying surgery after SCRT is safe and results in higher rates of tumor downstaging, SCRT is rarely recommended in the USA. The optimal timing of surgery remains uncertain, and there is growing interest in further improving outcomes by incorporating chemotherapy with neoadjuvant radiation.

Compliance with Ethical Guidelines

Conflict of Interest Stephanie M. Yoon declares no potential conflicts of interest.

Percy Lee has received grants, personal fees, and non-financial support from Viewray, Inc. and AstraZeneca, Inc., along with personal fees from Varian, Inc.

Ann Raldow is a consultant for Intelligent Automation, Inc., and has received travel accommodations and honorarium from Varian Medical Systems.

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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Society AC. Key statistics for colorectal Cancer. 2019.
2. Guidelines NCP. Rectal cancer. 2019;Version 2.2019.
3. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24(28):4620–5. https://doi.org/10.1200/jco.2006.06.7629.
4. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40. https://doi.org/10.1056/NEJMoa040694.
5. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–33. https://doi.org/10.1200/jco.2011.40.1836.
6. Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–7. https://doi.org/10.1056/nejm199704033361402.
7. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644–50. https://doi.org/10.1200/jco.2005.08.144.

8. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46. https://doi.org/10.1056/NEJMoa010580.
9. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575–82. https://doi.org/10.1016/s1470-2045(11)70097-3.
10. Couwenberg AM, Burbach JPM, Intven MPW, Consten ECJ, Schiphorst AHW, Smits AB, et al. Health-related quality of life in rectal cancer patients undergoing neoadjuvant chemoradiation with delayed surgery versus short-course radiotherapy with immediate surgery: a propensity score-matched cohort study. Acta Oncol. 2019;58(4):407–16. https://doi.org/10.1080/0284186x.2018.1551622.
11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23. https://doi.org/10.1002/bjs.5506.
12. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol. 2004;72(1):15–24. https://doi.org/10.1016/j.radonc.2003.12.006.
13. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: trans-Tasman radiation oncology group trial 01.04. J Clin Oncol. 2012;30(31):3827–33. https://doi.org/10.1200/jco.2012.42.9597.
14. Ansari N, Solomon MJ, Fisher RJ, Mackay J, Burmeister B, Ackland S, et al. Acute adverse events and postoperative complications in a randomized trial of preoperative short-course radiotherapy versus long-course chemoradiotherapy for T3 adenocarcinoma of the rectum: trans-Tasman radiation oncology group trial (TROG 01.04). Ann Surg. 2017;265(5):882–8. https://doi.org/10.1097/sla.0000000000001987.
15.•• Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336–46. https://doi.org/10.1016/s1470-2045(17)30086-4 **Important RCT evaluating optimal neoadjuvant radiation and its timing after surgery. Confirmed no difference in oncologic outcomes between SCRT and long-course radiation. Also demonstrated that delaying surgery after SCRT improves tumor downstaging**.
16. Rombouts AJM, Hugen N, Verhoeven RHA, Elferink MAG, Poortmans PMP, Nagtegaal ID, et al. Tumor response after long interval comparing 5x5Gy radiation therapy with chemoradiation therapy in rectal cancer patients. Eur J Surg Oncol. 2018;44(7):1018–24. https://doi.org/10.1016/j.ejso.2018.03.017.
17. Latkauskas T, Pauzas H, Kairevice L, Petrauskas A, Saladzinskas Z, Janciauskiene R, et al. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. BMC Cancer. 2016;16(1):927. https://doi.org/10.1186/s12885-016-2959-9.
18. Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PC, Kenady DE, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys. 2000;46(4):883–8. https://doi.org/10.1016/s0360-3016(99)00486-1.
19. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331(8):502–7. https://doi.org/10.1056/nejm199408253310803.
20. Pettersson D, Lorinc E, Holm T, Iversen H, Cedermark B, Glimelius B, et al. Tumour regression in the randomized Stockholm III trial of radiotherapy regimens for rectal cancer. Br J Surg. 2015;102(8):972–8; discussion 8. https://doi.org/10.1002/bjs.9811.
21.• Erlandsson J, Lorinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B, et al. Tumour regression after radiotherapy for rectal cancer - results from the randomised Stockholm III trial. Radiother Oncol. 2019;135:178–86. https://doi.org/10.1016/jradonc201903016 **Additional results from Stockholm III Trial suggest that SCRT and delayed surgery may improve pathologic complete response rates**.
22. Dutta SW, Alonso CE, Jones TC, Waddle MR, Janowski EM, Trifiletti DM. Short-course versus long-course neoadjuvant therapy for non-metastatic rectal cancer: patterns of care and outcomes from the National Cancer Database. Clin Colorectal Cancer. 2018;17(4):297–306. https://doi.org/10.1016/j.clcc.2018.07.008.
23. Hoendervangers S, Couwenberg AM, Intven MPW, van Grevenstein WMU, Verkooijen HM. Comparison of pathological complete response rates after neoadjuvant short-course radiotherapy or chemoradiation followed by delayed surgery in locally advanced rectal cancer. Eur J Surg Oncol. 2018;44(7):1013–7. https://doi.org/10.1016/j.ejso.2018.03.014.
24. Lupattelli M, Lancellotta V, Montesi G, Bini V, Castellani D, Falcinelli L, et al. Short-course radiotherapy with delayed surgery in unfit locally advanced rectal cancer patients. Int J Color Dis. 2016;31(6):1233–4. https://doi.org/10.1007/s00384-015-2441-1.
25. Raoof M, Nelson RA, Nfonsam VN, Warneke J, Krouse RS. Prognostic significance of lymph node yield in ypN0 rectal cancer. Br J Surg. 2016;103(12):1731–7. https://doi.org/10.1002/bjs.10218.
26. Beppu N, Kobayashi M, Matsubara N, Noda M, Yamano T, Doi H, et al. Comparison of the pathological response of the mesorectal positive nodes between short-course chemoradiotherapy with delayed surgery and long-course chemoradiotherapy in patients with rectal cancer. Int J Color Dis. 2015;30(10):1339–47. https://doi.org/10.1007/s00384-015-2321-8.
27. Park IJ, You YN, Agarwal A, Skibber JM, Rodriguez-Bigas MA, Eng C, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol. 2012;30(15):1770–6. https://doi.org/10.1200/jco.2011.39.7901.
28. Swellengrebel HA, Bosch SL, Cats A, Vincent AD, Dewit LG, Verwaal VJ, et al. Tumour regression grading after chemoradiotherapy for locally advanced rectal cancer: a near pathologic complete response does not translate into good clinical outcome. Radiother Oncol. 2014;112(1):44–51. https://doi.org/10.1016/j.radonc.2014.05.010.
29. Rose BS, Winer EP, Mamon HJ. Perils of the pathologic complete response. J Clin Oncol. 2016;34(33):3959–62. https://doi.org/10.1200/jco.2016.68.1718.
30. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114–23. https://doi.org/10.1056/NEJMoa060829.
31. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008;26(22):3687–94. https://doi.org/10.1200/jco.2007.15.3858.

32. Bujko K, Sopylo R. Short-course radiotherapy with delayed surgery for rectal cancer: a third option. Lancet Oncol. 2017;18(3):275–6. https://doi.org/10.1016/s1470-2045(17)30075-x.
33. Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P. Chaisemartin cd et al. effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). J Clin Oncol. 2016;34(31):3773–80. https://doi.org/10.1200/jco.2016.67.6049.
34. Kaytan-Saglam E, Balik E, Saglam S, Akgun Z, Ibis K, Keskin M, et al. Delayed versus immediate surgery following short-course neoadjuvant radiotherapy in resectable (T3N0/N+) rectal cancer. J Cancer Res Clin Oncol. 2017;143(8):1597–603. https://doi.org/10.1007/s00432-017-2406-6.
35. Kwak YK, Kim K, Lee JH, Kim SH, Cho HM, Kim DY, et al. Timely tumor response analysis after preoperative chemoradiotherapy and curative surgery in locally advanced rectal cancer: a multi-institutional study for optimal surgical timing in rectal cancer. Radiother Oncol. 2016;119(3):512–8. https://doi.org/10.1016/j.radonc.2016.03.017.
36. Wiltink LM, Nout RA, van der Voort van Zyp JR, Ceha HM, Fiocco M, Meershoek-Klein Kranenbarg E, et al. Long-term health-related quality of life in patients with rectal cancer after preoperative short-course and long-course (chemo) radiotherapy. Clin Colorectal Cancer. 2016;15(3):e93–9. https://doi.org/10.1016/j.clcc.2016.02.012.
37. Couwenberg AM, Burbach JPM, van Grevenstein WMU, Smits AB, Consten ECJ, Schiphorst AHW, et al. Effect of neoadjuvant therapy and rectal surgery on health-related quality of life in patients with rectal cancer during the first 2 years after diagnosis. Clin Colorectal Cancer. 2018;17(3):e499–512. https://doi.org/10.1016/j.clcc.2018.03.009.
38. Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. Clin Colorectal Cancer. 2015;14(2):106–14. https://doi.org/10.1016/j.clcc.2014.12.007.
39. Russell MM, Ganz PA, Lopa S, Yothers G, Ko CY, Arora A, et al. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04. Ann Surg. 2015;261(1):144–8. https://doi.org/10.1097/sla.0000000000000594.
40. Nasvall P, Dahlstrand U, Lowenmark T, Rutegard J, Gunnarsson U, Strigard K. Quality of life in patients with a permanent stoma after rectal cancer surgery. Qual Life Res. 2017;26(1):55–64. https://doi.org/10.1007/s11136-016-1367-6.
41. Raldow AC, Chen AB, Russell M, Lee PP, Hong TS, Ryan DP, et al. Cost-effectiveness of short-course radiation therapy vs long-course chemoradiation for locally advanced rectal cancer. JAMA Netw Open. 2019;2(4):e192249. https://doi.org/10.1001/jamanetworkopen.2019.2249.
42. Mowery YM, Salama JK, Zafar SY, Moore HG, Willett CG, Czito BG, et al. Neoadjuvant long-course chemoradiation remains strongly favored over short-course radiotherapy by radiation oncologists in the United States. Cancer. 2017;123(8):1434–41. https://doi.org/10.1002/cncr.30461.
43. Abdel-Rahman O, Elhalawani HM, Allen PK, Holliday EB. Utilization of short-course radiation therapy for patients with nonmetastatic rectal adenocarcinoma in the United States. Adv Radiat Oncol. 2018;3(4):611–20. https://doi.org/10.1016/j.adro.2018.07.007.
44. Haque W, Verma V, Butler EB, Teh BS. Trends and disparities in the utilization of hypofractionated neoadjuvant radiation therapy for rectal cancer in the United States. J Gastrointest Oncol. 2018;9(4):601–9. https://doi.org/10.21037/jgo.2018.05.08.
45. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst. 2015;107(11). https://doi.org/10.1093/jnci/djv248.
46. Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2015;16(8):979–89. https://doi.org/10.1016/s1470-2045(15)00159-x.
47. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol. 2012;30(36):4558–65. https://doi.org/10.1200/jco.2012.42.8771.
48. Schmoll H-J, Haustermans K, Price TJ, Nordlinger B, Hofheinz R, Daisne J-F, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/− oxaliplatin in locally advanced rectal cancer: final results of PETACC-6. J Clin Oncol. 2018;36(15_suppl):3500. https://doi.org/10.1200/JCO.2018.36.15_suppl.3500.
49. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011;29(20):2773–80. https://doi.org/10.1200/jco.2010.34.4911.
50. Horisberger K, Treschl A, Mai S, Barreto-Miranda M, Kienle P, Strobel P, et al. Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: results of a phase II MARGIT trial. Int J Radiat Oncol Biol Phys. 2009;74(5):1487–93. https://doi.org/10.1016/j.ijrobp.2008.10.014.
51. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. 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 (EXPERT-C). J Clin Oncol. 2012;30(14):1620–7. https://doi.org/10.1200/jco.2011.39.6036.
52. Sun PL, Li B, Ye QF. Effect of neoadjuvant cetuximab, capecitabine, and radiotherapy for locally advanced rectal cancer: results of a phase II study. Int J Color Dis. 2012;27(10):1325–32. https://doi.org/10.1007/s00384-012-1446-2.
53. Valentini V, De Paoli A, Gambacorta MA, Mantini G, Ratto C, Vecchio FM, et al. Infusional 5-fluorouracil and ZD1839 (Gefitinib-Iressa) in combination with preoperative radiotherapy in patients with locally advanced rectal cancer: a phase I and II trial (1839IL/0092). Int J Radiat Oncol Biol Phys. 2008;72(3):644–9. https://doi.org/10.1016/j.ijrobp.2008.01.046.
54. Helbling D, Bodoky G, Gautschi O, Sun H, Bosman F, Gloor B, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol. 2013;24(3):718–25. https://doi.org/10.1093/annonc/mds519.
55. Dellas K, Hohler T, Reese T, Wurschmidt F, Engel E, Rodel C, et al. Phase II trial of preoperative radiochemotherapy with concurrent bevacizumab, capecitabine and oxaliplatin in patients with locally advanced rectal cancer. Radiat Oncol. 2013;8(90). https://doi.org/10.1186/1748-717x-8-90.
56. Yeo SG, Oh JH, Kim DY, Baek JY, Kim SY, Park JW, et al. Preoperative short-course concurrent chemoradiation therapy

followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). Int J Radiat Oncol Biol Phys. 2013;86(1):34–9. https://doi.org/10.1016/j.ijrobp.2012.11.018.

57. Chung MJ, Kim DW, Chung WK, Lee SH, Jeong SK, Hwang JK, et al. Preoperative short- vs. long-course chemoradiotherapy with delayed surgery for locally advanced rectal cancer. Oncotarget. 2017;8(36):60479–86. https://doi.org/10.18632/oncotarget.10280.
58. Lee JH, Kim JG, Oh ST, Lee MA, Chun HG, Kim DY, et al. Two-week course of preoperative chemoradiotherapy followed by delayed surgery for rectal cancer: a phase II multi-institutional clinical trial (KROG 11-02). Radiother Oncol. 2014;110(1):150–4. https://doi.org/10.1016/j.radonc.2013.11.013.
59. Brooks S, Glynne-Jones R, Novell R, Harrison M, Brown K, Makris A. Short course continuous, hyperfractionated, accelerated radiation therapy (CHART) as preoperative treatment for rectal cancer. Acta Oncol. 2006;45(8):1079–85. https://doi.org/10.1080/02841860600897900.
60. Widder J, Herbst F, Dobrowsky W, Schmid R, Pokrajac B, Jech B, et al. Preoperative short-term radiation therapy (25 Gy, 2.5 Gy twice daily) for primary resectable rectal cancer (phase II). Br J Cancer. 2005;92(7):1209–14. https://doi.org/10.1038/sj.bjc.6602485.
61. Beppu N, Kimura F, Okamoto R, Nakamoto Y, Tomita N, Yanagi H, et al. Early results of a phase-II study of modified short-course radiotherapy combined with capecitabine and delayed surgery for T3M0 lower rectal cancer. Acta Oncol. 2018;57(6):860–2. https://doi.org/10.1080/0284186x.2017.1410286.
62. Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol. 2006;24(4):668–74. https://doi.org/10.1200/jco.2005.04.4875.
63. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol. 2010;11(3):241–8. https://doi.org/10.1016/s1470-2045(09)70381-x.
64. Fernandez-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol. 2010;28(5):859–65. https://doi.org/10.1200/jco.2009.25.8541.
65. Gollins S, West N, Sebag-Montefiore D, Susnerwala S, Falk S, Brown N, et al. A prospective phase II study of pre-operative chemotherapy then short-course radiotherapy for high risk rectal cancer: COPERNICUS. Br J Cancer. 2018;119(6):697–706. https://doi.org/10.1038/s41416-018-0209-4.
66. Aghili M, Sotoudeh S, Ghalehtaki R, Babaei M, Farazmand B, Fazeli MS, et al. Preoperative short course radiotherapy with concurrent and consolidation chemotherapies followed by delayed surgery in locally advanced rectal cancer: preliminary results. Radiat Oncol J. 2018;36(1):17–24. https://doi.org/10.3857/roj.2017.00185.
67. Bisschop C, van Dijk TH, Beukema JC, Jansen RLH, Gelderblom H, de Jong KP, et al. Short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical treatment in primary stage IV rectal cancer: long-term results of a phase II study. Ann Surg Oncol. 2017;24(9):2632–8. https://doi.org/10.1245/s10434-017-5897-0.
68. Myerson RJ, Tan B, Hunt S, Olsen J, Birnbaum E, Fleshman J, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys. 2014;88(4):829–36. https://doi.org/10.1016/j.ijrobp.2013.12.028.
69. Olsen JR, Parikh PJ, Hunt S, Tan B, Myerson RJ. Sequential short course radiation and FOLFOX as preoperative therapy for rectal cancer: favorable LC, PFS, and QOL at 2 years. Int J Radiat Oncol Biol Phys. 2013;87(2):S88. https://doi.org/10.1016/j.ijrobp.2013.06.227.
70. Jia AY, Narang A, Safar B, Zaheer A, Murphy A, Azad NS, et al. Sequential short-course radiation therapy and chemotherapy in the neoadjuvant treatment of rectal adenocarcinoma. Radiat Oncol. 2019;14(1):147. https://doi.org/10.1186/s13014-019-1358-1.
71. Markovina S, Youssef F, Roy A, Aggarwal S, Khwaja S, DeWees T, et al. Improved metastasis- and disease-free survival with preoperative sequential short-course radiation therapy and FOLFOX chemotherapy for rectal cancer compared with neoadjuvant long-course chemoradiotherapy: results of a matched pair analysis. Int J Radiat Oncol Biol Phys. 2017;99(2):417–26. https://doi.org/10.1016/j.ijrobp.2017.05.048.
72. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Krynski J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27(5):834–42. https://doi.org/10.1093/annonc/mdw062.
73. Jin J, Tang Y, Liu S, Zhu Y, Wang W, Li G, et al. 496PShort-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR): a planned interim analysis. Ann Oncol. 2018;29(suppl_8). https://doi.org/10.1093/annonc/mdy281.043.
74. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol. 2016;34(27):3300–7. https://doi.org/10.1200/jco.2016.66.6198.
75. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. J Clin Oncol. 2019;37(34):3223–33. https://doi.org/10.1200/jco.18.02309.