Seminars in Colon and Rectal Surgery 30 (2019) 63–67

Contents lists available at ScienceDirect

Seminars in Colon and Rectal Surgery

journal homepage: www.elsevier.com/locate/yscrs

Total neoadjuvant therapy for rectal cancer

Steven R. Hunt, MD

Washington University School of Medicine, Department of Surgery, Section of Colon and Rectal Surgery, Campus Box 8109, St Louis, MO 63110, United States

ARTICLE INFO

Keywords:
Rectal cancer
Total neoadjuvant therapy
Neoadjuvant chemotherapy

ABSTRACT

The established standard of care in the treatment of locally advanced rectal cancer is trimodal therapy with neoadjuvant radiation, surgery and adjuvant chemotherapy. While the data supporting neoadjuvant radiation and surgery is well founded, there is little to no evidence that shows a benefit from adjuvant chemotherapy. The majority of cancer related deaths from rectal cancer are due to distant metastatic disease. Extrapolation from colon cancer data and small studies suggest that earlier administration of chemotherapy may improve outcomes. This article provides the background and theoretical arguments for the delivery of chemotherapy in the neoadjuvant setting. It will discuss early results, longer term outcomes, and future directions of neoadjuvant chemotherapy for locally advanced rectal cancer.

Introduction

Trimodality therapy combining pelvic radiation, surgery and chemotherapy is the current standard of care for patients with locally advanced rectal cancer (LARC). Over the last several decades, improvements in surgical techniques and the selective use of neoadjuvant radiation have dramatically improved the local recurrence rates for this disease. Historical rates of local recurrence for LARC were upwards of 25%, but these strategies have yielded consistently low rates of between 5% and 10%.[1–4] Despite these improvements, neoadjuvant radiation and optimal surgery have not shown consistent survival benefits.[5–7] Patients with LARC currently have a 30–35% risk of distant metastatic recurrence, which is the most frequent cause of cancer related death in this population.[4,8] Recent efforts to decrease the rate of distant recurrence have focused on delivering both radiotherapy and systemic chemotherapy in the neoadjuvant setting, a strategy known as total neoadjuvant therapy (TNT).

Background

The Swedish Rectal Cancer Trial proved that neoadjuvant radiation dramatically improved local recurrence rates for LARC.[2] This study showed a greater than 50% reduction in local recurrence, but was widely criticized because of the high local recurrence rate (27%) in the surgery only group. Critics pointed to Heald's excellent results with surgery alone, and surmised that radiation only compensated for inadequate operative techniques.[1] The Dutch Rectal Cancer Trail standardized surgery, mandated total mesorectal excision (TME) and still showed that the addition of neoadjuvant radiation reduced local recurrence by more than 50%.[9] The advantages of neoadjuvant delivery of radiation were supported in the German trial that compared preoperative and postoperative long course chemoradiation.[7] While only the German study used long course chemoradiation, these foundation trials were instrumental in establishing our current American trimodal therapy regimen.

While the advantage of adjuvant chemotherapy in the treatment of stage III colon cancer has been proven, the survival benefit for adjuvant chemotherapy in LARC has not been well-demonstrated in the era of trimodal therapy.[3,10–12]

The largest prospective randomized trial of adjuvant chemotherapy after neoadjuvant radiation and surgery was the EORTC trial. This four armed study aimed to answer two questions. First, is there an advantage to adding radiosensitizing fluorouracil to the neoadjuvant radiation regimen? Secondly, is there an advantage to adjuvant fluorouracil and leucovorin chemotherapy in patients who received neoadjuvant radiation? While the findings in this study did support the use of radiosensitizing chemotherapy in the neoadjuvant setting, there was no demonstrated survival benefit with adjuvant chemotherapy.[3,13,14] Subgroup analysis found that patients that had clinical downstaging of their primary tumors (ypT0-2) were the only patients to benefit from chemotherapy with improved disease free survival (DFS) and overall survival (OS).[15]

Several other trials have attempted to demonstrate the benefits of postoperative chemotherapy as an adjunct to preoperative radiation and surgery. These trials either failed to demonstrate an advantage, or were closed early due to poor accrual.[6,12,16] One common theme among these trials is poor compliance with adjuvant chemotherapy. Completion rates for planned chemotherapy ranged from 43% to 74% in these trials.

As opposed to the definitive data supporting the use of adjuvant oxaliplatin, fluorouracil, and leucovorin (FOLFOX) in colon cancer, the

E-mail address: hunts@wustl.edu

https://doi.org/10.1053/j.scrs.2019.04.004
1043-1489/

majority of the negative trials in rectal cancer treated patients with only fluorouracil and leucovorin, without oxaliplatin. It is reasonable to extrapolate colon cancer data to the adjuvant treatment of rectal cancer, and the National Comprehensive Cancer Network (NCCN) guidelines for rectal cancer reflect this. Large national database trails and systematic reviews have provided some evidence that patients would realize a survival benefit from adjuvant FOLFOX chemotherapy.[17–19] One British study that attempted to randomize patients to adjuvant capecitabine and oxaliplatin (CAPOX) or observation was closed due to poor accrual, presumptively because oncologists were uncomfortable with the randomization to the observation group given the definitive benefit of adjuvant therapy for colon cancer.[16]

One prospective randomized trial that did show a benefit with FOLFOX for patients with LARC was the ADORE trial in Korea.[20] Rather than enrolling patients at the initiation of therapy, this trial selected for tumors that had a poor response to neoadjuvant CRT. The study randomized patients with pathologic stage II or III rectal cancers after standard long course CRT and surgery to adjuvant chemotherapy with either fluorouracil/leucovorin or FOLFOX. The authors demonstrated a significant 3 year DFS advantage in the patients treated with FOLFOX. It is noteworthy that 96% of patients in this study completed all of their planned chemotherapy.

In the United States, the current standard of care in the treatment of LARC is neoadjuvant long course chemoradiation (CRT) followed by extirpative surgery and then adjuvant chemotherapy with FOLFOX. The CRT is delivered over 5.5 weeks and the usual waiting period before surgery is 6–8 weeks. Adjuvant chemotherapy is generally delivered at least one month after an uncomplicated surgery, and later if there are postoperative complications. Under the current standard treatment, in the best circumstances, adjuvant FOLFOX is delivered 4–5 months after the initiation of multimodality therapy. Such a delay in systemic chemotherapy would be unacceptable in colon cancer, as a systematic review demonstrated that a delay in the initiation of adjuvant chemotherapy had an adverse effect on cancer specific survival.[21] The authors found that for every month that treatment was delayed, the relative OS decreased by 14%. By extrapolation, delivering systemic chemotherapy in the neoadjuvant setting for LARC should lead to improved survival.

A pathologic complete response (pCR) after neoadjuvant radiation has long been used as a surrogate for the effectiveness of various treatment regimens. In most studies of traditional long course chemoradiation followed by a 6–8 week waiting period before surgery, pCR rates cluster around 20%.[22–24] It is well documented that a patient with a pCR has improved cancer specific outcomes with decreased local recurrence and improved disease free survival.[23–25] It is also clear that waiting longer to operate after the completion of long course CRT leads to a higher pCR rate.[26–31] While a pCR does portend a better oncologic outcome, it appears that this is a marker for a biologically more favorable tumor, rather than a goal unto itself. The Lyon R90-01 trial, which is another of the foundation trials that supports our current standard of care in LARC, showed that the longer wait increases pCR, but it does not have any influence on outcomes.[32] While waiting longer for surgery after CRT may achieve a higher percentage of patients with a pCR, there is no good evidence that the longer wait achieves better outcomes, only better prognostication. At best, the act of waiting longer merely allows us to identify the patients who are going to do well by virtue of attaining a pCR.

Total neoadjuvant therapy – early results

The initial studies that provided the proof of concept for TNT were driven by two motives: better oncologic outcomes and organ sparing (watch and wait) approaches. It was felt that preoperative chemotherapy would lead to better tolerance – one of the problems noted in the negative studies of adjuvant therapy in LARC. Additionally, earlier treatment would allow for sterilization of micrometastatic disease at a time when it is theoretically more vulnerable.[21] Neoadjuvant chemotherapy has been shown to be beneficial in the treatment of gastric cancer and colorectal liver metastases.[33,34] At the same time, a growing body of literature suggests that eliminating extirpative surgery was possible with rectal cancers that achieved a complete clinical response to neoadjuvant chemoradiation.[35,36] Because the proportion of patients with a pathologic complete response after CRT was relatively small (~20%), the hope was that the addition of neoadjuvant chemotherapy, and consequently a longer preoperative time interval, would lead to a substantially higher rate of complete responders. In theory, this would improve cancer specific outcomes and allow for selective non operative management.

One of the earliest reports of a TNT regimen was from Habr-Gama et al., who were pioneers of the watch and wait approach. A relatively small number of patients with low rectal cancers were treated with 50.4 Gy of pelvic radiation and six cycles of fluorouracil and leucovorin (three cycles were concomitant to radiation). They reported a 65% complete clinical response rate and an impressive 97% completion of therapy.[37]

The Spanish GCR-3 trial was a TNT trial evaluating four cycles of induction CAPOX chemotherapy followed by chemoradiation and surgery. The study compared this regimen to the classic chemoradiation, surgery and adjuvant chemotherapy in a randomized fashion. They enrolled 108 patients in the trial and reported their early results in 2010.[38] In the initial publication, they had similar rates of pCR (13.5% vs 14.3%), downstaging, tumor regression, and R0 resection. There was a significant difference in the percentage of patients who completed the chemotherapy protocol, favoring the TNT regimen (91% vs 54%, $p < 0.0001$). The toxicity during chemotherapy also favored the TNT regimen.

In what has come to be known as the "Timing Trial," Garcia-Aguilar et al. conducted a phase 2 multicenter non-randomized trial of sequential patient groups treated with neoadjuvant CRT and increasing time intervals and cycles of chemotherapy prior to TME. The authors evaluated 259 patients with clinical stage II and III rectal cancers. The first group of patients served as a control group, receiving CRT followed by surgery at 6–8 weeks. Subsequently, the next groups received 2, 4, or 6 cycles of FOLFOX at 2 week intervals between CRT and surgery. With increasing numbers of chemotherapy cycles, patients waited longer between chemotherapy and surgery – up to 20 weeks for patients in the group treated with 6 cycles of neoadjuvant chemotherapy. With more than 60 patients in each group, the authors demonstrated that increased time and number of FOLFOX cycles correlated with a significant increase in the pCR rates (Table 1).[22] While the 18% pCR rate for the control group was in agreement with historical data, the patients that received 6 cycles of neoadjuvant chemotherapy had a 38% rate of pCR. Importantly, there was no difference in surgical complications or technical difficulty between the groups; and no patients had progression of disease during the course of treatment – addressing two of the perceived concerns with a prolonged waiting period before surgery.

In a smaller single institution series, Myerson et al. treated patients with clinical stage II-IV rectal cancer with short course radiation (5 fractions of 5 GY over 5 days) followed by four cycles of FOLFOX chemotherapy prior to TME surgery. With 76 patients enrolled

Table 1
Data from the timing trial.[22] Pathologic complete response rates at surgery for patients with rectal cancer treated with variable cycles of neoadjuvant chemotherapy between chemoradiation and surgery ($p = 0.0036$).

	Group 1 ($n = 60$) no chemo	Group 2 ($n = 67$) 2 cycles FOLFOX	Group 3 ($n = 67$) 4 cycles FOLFOX	Group 4 ($n = 65$) 6 cycles FOLFOX
pCR (%)	18%	25%	30%	38%

in this pilot study, the authors demonstrated a 28% pCR rate.[39] The authors did not evaluate the technical difficulty of the surgical procedure, but the authors were able to achieve R0 resections in 95% of patients.

Some authors have suggested that radiation is not necessary if the primary tumor is not T4 and does not encroach on the mesorectal fascia by MRI. Schrag et al. conducted a small pilot study to evaluate induction chemotherapy with the selective use of CRT.[40] In this trial, patients with stage II and III tumors that were confined to the mesorectum were treated with six cycles of FOLFOX with bevacizumab for cycles 1–4. Patients were then restaged and neoadjuvant CRT was recommended only if the tumor did not respond or if the patient did not tolerate chemotherapy. Thirty-two patients were entered in the trail. Two patients did not tolerate chemotherapy and received neoadjuvant CRT. Of the patients that completed the neoadjuvant chemotherapy, none required neoadjuvant CRT. The pCR rate of these patients was 25%. There were no local failures and DFS was 84% at 4 years.

Total neoadjuvant therapy – long term outcomes

While complete tumor responses and R0 resections are good surrogates for the efficacy of TNT therapy, the goal of treatment is to improve long term, disease specific and overall survival. Without demonstrated improvements in these outcomes, TNT's only value would be earlier completion of therapy.

The Spanish GCR-3 trial's long term oncologic outcomes disappointed many advocates of TNT therapy. Despite a significant and highly disparate difference in the number of patients who completed the chemotherapy regimen, the 5 year actuarial results of the TNT and traditional CRT groups showed no difference in DFS (62% vs 64%, $p = 0.85$), OS (75% vs 78%, $p = 0.64$), local recurrence (5% vs 2%, $p = 0.61$), or distant metastatic disease (23% vs 21%, $p = 0.79$).[41]

While the original timing trial was only powered to evaluate pCR rates, the patients in Garcia-Aguilar's study were followed for long term oncologic outcomes. Again, this prospective study compared sequential groups of patients treated with incrementally increased dosing regimens of CRT and chemotherapy in the neoadjuvant setting. The authors demonstrated that disease free survival was significantly associated with ypTNM stage, study group, and pCR[42] (see Table 2). Interestingly, the number of neoadjuvant chemotherapy cycles did not seem to have a dose related effect on cancer specific outcomes. This is in contrast to the group's earlier findings that an increased number of neoadjuvant chemotherapy cycles lead to an increased rate of pCR.

Of the patients in the control group treated with traditional neoadjuvant chemoradiation, surgery, and then adjuvant chemotherapy, only 69% received any chemotherapy. In order to demonstrate that the survival differences were attributable to the neoadjuvant delivery of chemotherapy, the authors did a subgroup evaluation only of patients who received ≥1 cycle chemotherapy. Again, disease free survival significantly favored the patients who were in the neoadjuvant chemotherapy group.

Importantly, regardless of treatment group, staging at surgery was significantly associated with both disease free and overall survival in a dose related manner. Patients that had a pCR had a 94% actuarial 5 year DFS, while those with yp stage III disease had a 51% 5 year DFS. This lends credence to the observation that the biology of the tumor is the most important determinant of outcome. Regardless, this study suggests that TNT can help to exploit certain biologically susceptible cancers.

Markovina et al. evaluated the long term oncologic results of the patients who were treated in the short course TNT pilot discussed previously. They performed a matched pair analysis comparing patients treated in the short course TNT pilot study to patients treated with conventional neoadjuvant CRT and adjuvant chemotherapy.[43] Compared to patients treated with conventional trimodal therapy, the patients that received short course TNT had significantly improved 3 year disease free survival (68% vs 85% DFS at 3 years, $p = 0.032$) and distant metastasis-free survival (70% vs 88% DMFS at 3 years, $p = 0.028$). There was no difference in local control or overall survival between the two groups.

Memorial Sloan Kettering performed a cohort analysis on their patients who received TNT therapy to those treated with traditional neoadjuvant chemoradiation and adjuvant chemotherapy. As part of their practice, patients who had a complete clinical response were observed in a watch and wait protocol. Consistent with prior studies, they found that the patients in the TNT cohort received significantly more cycles of chemotherapy with fewer dose reductions.[44] The authors combined the complete clinical responders who were observed with those patients found to have a complete pathological response at surgery. In their analysis, patients in the TNT group had a complete response rate of 36%, compared to a 21% complete response rate in those receiving traditional trimodal therapy. No long term oncologic outcomes were reported in this study.

Table 2
Long term oncologic results from the timing trail evaluating patients that received a variable number of cycles of neoadjuvant chemotherapy after neoadjuvant chemoradiation.

ypTNM stage	5 year DFS (%)	*p* Value
0	94	<0.0001
I	88	
II	60	
III	51	
Pathologic complete response		
No	69	0.0001
Yes	96	
Study group		
Control	50	0.004
2 cycles FOLFOX	81	
4 cycles FOLFOX	86	
6 cycles FOLFOX	76	

Current trials

There are currently 3 large ongoing trials that should contribute to our growing experience with TNT for rectal cancer. Two of these trials compare traditional long course neoadjuvant chemoradiation, surgery and adjuvant chemotherapy to TNT regimens, and should provide evidence as to the efficacy of TNT. Each study uses different styles of TNT delivery and they should, therefore, provide some guidance as to the proper order and delivery method of chemotherapy and radiation. All of these trials are designed to evaluate long term oncologic outcomes.

RAPIDO is primarily a European trial comparing traditional trimodal treatment to TNT using short course radiation (5 Gy delivered over 5 days) followed by neoadjuvant CAPOX and then surgery. Interestingly, this trial seeks patients with advanced tumors that are at high risk for local and distant failure. The inclusion criteria for tumors require T4 or N2 tumors or involvement of the mesorectal fascia. RAPIDO will test the theory that short course radiation is safe as part of a TNT protocol. The authors hypothesize that the shorter course of radiation, combined with a short waiting period before the initiation of chemotherapy will have a positive impact on long term oncologic outcomes by initiating chemotherapy sooner.

The PROSPECT trial is a prospective randomized clinical trial comparing conventional trimodal therapy to neoadjuvant chemotherapy with selective use of neoadjuvant chemoradiation for patients whose tumors do not shrink with the neoadjuvant chemotherapy. If the primary tumor has a 20% reduction in size, the patient foregoes chemoradiation and has a TME. In contrast to the RAPIDO trial, PROSPECT tumors are relatively good prognostic cancers. To be eligible for the trial, tumors must be T3 without bulky nodal disease (N0 or N1) and

candidates for a low anterior resection based on tumor height. This trial will test the hypothesis that selective use of radiation as part of a TNT regimen is safe and effective.

While the study is designed to test the feasibility of the watch and wait strategy after TNT therapy, the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial will allow comparison of two different TNT strategies. In this trail, patients will be randomized to induction therapy (with chemotherapy first) or consolidation treatment (with chemoradiation followed by chemotherapy). Under this protocol, patients that have a complete clinical response are observed with serial exams and imaging. Those that have residual tumor are treated with TME. The OPRA trial allows inclusion of all stage II and III patients that have respectable disease. OPRA should provide significant insight into the appropriate sequencing of chemotherapy and radiation in a TNT protocol.

Summary

While the evidence supporting chemotherapy in the treatment of rectal cancer is not convincing, extrapolation from colon cancer studies suggests that chemotherapy should benefit patients with locally invasive rectal cancer. There are several possibilities as to why researchers have been unable to demonstrate a benefit from adjuvant chemotherapy in this population. The poor tolerance and long lag time to adjuvant chemotherapy are certainly two possibilities, and TNT could potentially overcome these shortcomings. While we await the results from the large prospective randomized studies, it is clear that TNT will offer some advantages over conventional trimodal therapy. The NCCN has recognized the importance of, and the heterogeneous approaches to TNT, and the new guidelines allow for almost any combination of trimodal therapy – both in the traditional delivery and as part of a TNT protocol.

Conflicts of Interest

None.

References

1 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. Jun 28 1986;1(8496):1479–1482.
2 Swedish Rectal Cancer T, Cedermark B, Dahlberg M, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*. Apr 3 1997;336(14):980–987.
3 Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. Sep 14 2006;355(11):1114–1123.
4 Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg*. Nov 2007;246(5):693–701.
5 Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol*. Feb 2015;16(2):200–207.
6 Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol*. Apr 2015;26(4):696–701.
7 Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. Oct 21 2004;351(17):1731–1740.
8 Sauer R, Liersch T, Merkel S, 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*. Jun 1 2012;30(16):1926–1933.
9 Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. Aug 30 2001;345(9):638–646.
10. Kuebler JP, Wieand HS, O'Connell MJ. et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*. 2007;25(16):2198–2204.
11. Andre T, Boni C, Navarro M. et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109–3116.
12 Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol*. Nov 2014;113(2):223–229.
13 Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results–EORTC 22921. *J Clin Oncol*. Aug 20 2005;23(24):5620–5627.
14 Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol*. Feb 2014;15(2):184–190.
15 Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. *J Clin Oncol*. Oct 1 2007;25(28):4379–4386.
16 Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol*. Jul 2014;25(7):1356–1362.
17 Zhao L, Liu R, Zhang Z, et al. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. *Colorectal Dis*. Aug 2016;18(8):763–772.
18 Rosello S, Papaccio F, Roda D, Tarazona N, Cervantes A. The role of chemotherapy in localized and locally advanced rectal cancer: A systematic revision. *Cancer Treat Rev*. Feb 2018;63:156–171.
19 Margalit O, Mamtani R, Kopetz S, et al. Refining the Use of Adjuvant Oxaliplatin in Clinical Stage II or III Rectal Adenocarcinoma. *Oncologist* Jan 29 2019.
20 Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol*. Oct 2014;15(11):1245–1253.
21 Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA*. Jun 8 2011;305(22):2335–2342.
22 Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol*. Aug 2015;16(8):957–966.
23 Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum*. Mar 2003;46(3):298–304.
24 Kuo LJ, Liu MC, Jian JJ, et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy. *Ann Surg Oncol*. Oct 2007;14(10):2766–2772.
25 Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg*. Jul 2012;99(7):918–928.
26 Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol*. Aug 1999;17(8):2396.
27 Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol*. Oct 2008;15(10):2661–2667.
28 Wolthuis AM, Penninckx F, Haustermans K, et al. Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. *Ann Surg Oncol*. Sep 2012;19(9):2833–2841.
29 Pettersson D, Lorinc E, Holm T, et al. Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. *Br J Surg*. Jul 2015;102(8):972–978 discussion 978.
30 Probst CP, Becerra AZ, Aquina CT, et al. Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation. *J Am Coll Surg*. Aug 2015;221(2):430–440.
31 Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg*. Oct 2009;250(4):582–589.
32 Cotte E, Passot G, Decullier E, et al. Pathologic Response, When Increased by Longer Interval, Is a Marker but Not the Cause of Good Prognosis in Rectal Cancer: 17-year Follow-up of the Lyon R90-01 Randomized Trial. *Int J Radiat Oncol Biol Phys*. Mar 1 2016;94(3):544–553.
33 Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. Jul 6 2006;355(1):11–20.
34 Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. Mar 22 2008;371(9617):1007–1016.
35 Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg*. Oct 2004;240(4):711–717 discussion 717-718.
36 Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg*. Dec 2012;256(6):965–972.
37 Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for

distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum*. Dec 2009;52(12):1927–1934.
38 Fernandez-Martos C, Pericay C, Aparicio J, 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*. Feb 10 2010;28(5):859–865.
39 Myerson RJ, Tan B, Hunt S, 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*. Mar 15 2014;88(4):829–836.
40 Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. *J Clin Oncol*. Feb 20 2014;32(6):513–518.
41 Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trialdagger. *Ann Oncol*. Aug 2015;26(8):1722–1728.
42 Marco MR, Zhou L, Patil S, et al. Consolidation mFOLFOX6 Chemotherapy After Chemoradiotherapy Improves Survival in Patients With Locally Advanced Rectal Cancer: Final Results of a Multicenter Phase II Trial. *Dis Colon Rectum*. Oct 2018;61(10):1146–1155.
43 Markovina S, Youssef F, Roy A, 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*. Oct 1 2017;99(2):417–426.
44 Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. *JAMA Oncol*. Jun 14 2018;4(6):e180071.