28
Rectal Cancer: Neoadjuvant Therapy

Andrea Cercek and Julio Garcia-Aguilar

Key Concepts

- Neoadjuvant radiotherapy is associated with an improvement in local pelvic control following proctectomy for rectal cancer as compared to surgery alone.
- Neoadjuvant chemoradiotherapy is associated with an improvement in local pelvic control and has lower toxicity as compared to postoperative chemoradiotherapy.
- Short-course neoadjuvant radiotherapy has been demonstrated to have similar outcomes in terms of overall survival, disease-free survival, and local pelvic control when compared to long-course neoadjuvant chemoradiotherapy and is associated with lower cost and shorter time to multidrug systemic cytotoxic chemotherapy.
- Current research is focused on limiting the morbidity of therapy, by omitting either proctectomy or radiotherapy in select patients.

Introduction

Neoadjuvant therapy is a critical component of the multidisciplinary treatment of patients with rectal cancer. The objective of neoadjuvant therapy, either radiotherapy, combined chemoradiotherapy, or chemotherapy alone, is to reduce the risk of local recurrence in patients with locally advanced rectal cancer (LARC) undergoing surgical resection. But neoadjuvant therapy provides other potential advantages to rectal cancer patients. It allows early assessment of tumor responsiveness to therapy, which is closely correlated with long-term oncologic outcomes [1–3]. In addition, neoadjuvant therapy could potentially enable the consideration of organ preservation by allowing for more effective local excision and nonoperative management (NOM) strategies. Finally, delivering systemic chemotherapy before surgery in patients at risk for distant metastasis has the potential to improve survival by addressing micrometastatic disease earlier and improving treatment compliance. Maximizing neoadjuvant treatment response can therefore have a profound effect on both oncologic and quality-of-life outcomes.

In this chapter, we will focus primarily on neoadjuvant therapy for LARC, widely accepted to be clinical stage II (cT3–4, cN0) or stage III (any cT, cN1–2) invasive adenocarcinomas of the rectum. We will review various treatment paradigms and the data supporting each.

Historical Context

The story of neoadjuvant radiotherapy and chemoradiotherapy for patients suffering from rectal cancer is long and convoluted, and although much has been published on the topic, there is no universally agreed-upon treatment strategy. It is important for the reader to understand how we arrived at our current state of affairs so that the data from published trials can be put in the proper context.

The concept of neoadjuvant therapy for rectal cancer was first introduced by Janeway and Quick in c. 1917, who noted significant tumor response when gold filtered radon emanation seeds were implanted directly into rectal cancers [4]. In the era when the surgical mortality and morbidity for a rectal cancer operation was prohibitive, contact radiation with emanation seeds containing radium salts or radon was explored as a curative treatment. Surgery was considered a salvage procedure for patients with tumors resistant to radiation [5]. As surgery became safer and the limitations of contact radiation as the only treatment modality became apparent, radiation lost its role as a primary treatment and

A. Cercek, M.D.
Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

J. Garcia-Aguilar, M.D., Ph.D. (✉)
Department of Surgery, Memorial Sloan Kettering Cancer Center, 1233 York Avenue, New York, NY 10065, USA
e-mail: garciaaj@mskcc.org

S.R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, DOI 10.1007/978-3-319-25970-3_28

became an adjuvant to surgical resection. In fact, for many years, proctectomy alone became standard treatment for rectal cancer. It was eventually realized that the outcomes of surgery alone were often suboptimal, with 5-year local recurrence rates in published trials of 25–30 % [6–8]. It was demonstrated that adjuvant chemoradiotherapy improved oncologic outcomes, and in 1990 the National Institutes of Health advocated adjuvant external beam radiotherapy and chemotherapy for patients with stage II and stage III tumors [9]. In the United States, except for a few select referral centers, upfront proctectomy followed by selective postoperative chemoradiotherapy was the regimen utilized for most patients. However, postoperative radiotherapy is associated with relatively high toxicity and is poorly tolerated by many patients. Investigators in Europe and select US centers explored utilizing neoadjuvant radiotherapy and chemoradiotherapy, and eventually the benefits of administering radiotherapy in the preoperative period were demonstrated. In response to these data, many US clinicians simply moved the chemoradiotherapy package from the postoperative to the preoperative period. It is puzzling that, although much of the data demonstrating the benefits of neoadjuvant radiotherapy came from trials of short-course radiotherapy, and neoadjuvant short-course radiotherapy has been demonstrated to have similar oncologic outcomes as neoadjuvant long-course chemoradiotherapy in two prospective randomized trials [10, 11], the use of short-course radiotherapy has been limited in the United States.

At the same time that neoadjuvant radiotherapy was demonstrated to be more effective and less toxic than postoperative radiotherapy, there was a realization that oncologic outcomes following proctectomy for rectal cancer were highly technique dependent [12]. Wide variability in outcomes was seen, depending on who did the operation and how it was performed. So once again the wheel of opinion turned full circle, with some surgeons arguing that radiotherapy primarily compensated for“sloppy” surgery and that there was no need for the patient with non-fixed tumors to undergo radiotherapy if proctectomy was performed properly. Data from the Dutch Rectal Cancer trial and others, however, suggested that the oncologic benefits of neoadjuvant radiotherapy and good surgical technique were additive, not compensatory, with regard to pelvic control [13].

Clinicians are aware that therapies for rectal cancer are morbid and unfortunately the most effective treatment, proctectomy is associated witht he greatest chance of lasting morbidity. We continue to search for treatment regimens in which morbidity can be lessened while preserving the chance for cure, especially in patients with non-fixed tumors. Definitive chemoradiotherapy, or local excision +/− adjuvant chemoradiotherapy, would avoid proctectomy. Chemotherapy regimens are now more effective, and there is interest in upfront proctectomy in patients with mesorectal margins that are not threatened based on preoperative imaging followed by selective use of postoperative chemotherapy. In addition, there is interest in the use of neoadjuvant chemotherapy alone. Both of these strategies would avoid the toxicity of radiotherapy. Another approach that has been utilized extensively in Europe and in select US centers is to administer neoadjuvant short-course radiotherapy, followed by proctectomy and selective use of postoperative chemotherapy. The three aforementioned strategies allow the patient to receive effective systemic chemotherapy faster than the regimen commonly employed in the United States—long-course chemoradiotherapy (in which the patient receives only a radiosensitizing chemotherapeutic agent) followed by delayed proctectomy. This concept has intrinsic appeal, given that most patients with rectal cancer who ultimately fail treatment succumb to distant metastatic disease, not local pelvic recurrence, and that the benefit of neoadjuvant radiotherapy has primarily been to improve pelvic control without improvement in overall survival.

One of the difficulties in constructing guidelines for treatment of patients with rectal cancer is that treatment decisions must take into account multiple variables: tumor fixation, circumferential position in the rectum, relation to the pelvic floor musculature, pelvic morphology, clinical T and N stage, presence of symptoms, presence of metastases, continence status, planned operation, etc. It is virtually impossible to publish straightforward guidelines that account for all of these variables. At present, the clinician caring for the patient with rectal cancer must have a firm grasp of the rationale for, and the data supporting, any proposed treatment algorithm and be facile enough to tailor recommendations for therapy based on the characteristics of the patient and the tumor.

Postoperative Radiotherapy

Although currently out of favor, one of the advantages of the strategy of upfront proctectomy followed by selective chemoradiotherapy is that the exact stage of the tumor is known prior to initiation of radiotherapy, and radiation can be avoided in patients with early-stage tumors who may not derive benefit. A number of studies demonstrated that surgery followed by radiation, delivered in 180–200 cGy a day for a total dose of 45–50 Gy, was more effective than surgery alone in achieving local control in patients with stage II or III rectal cancer [14]. The Gastrointestinal Tumor Study Group (GITSG) trial was aimed to accrue 520 patients with rectal cancer located within 12 cm from the anal verge, extending to the perirectal fat or metastasizing to the regional lymph nodes, with no evidence of distant metastasis. After recovery from surgery, patients who had a complete resection were randomized to one of four arms: observation, postoperative radiation (40–48 Gy of total radiation in 1.8 or 2 Gy fractions), chemotherapy (bolus infusion 5-FU and semustine for 18 months), or radiation plus chemotherapy [6]. The study was terminated after 227 patients had been accrued because interim analysis showed statistical differences between

treatment arms. The combined modality therapy was superior to resection alone in preventing recurrence (33 % vs. 55 %; $p = 0.42$). Radiation and chemotherapy and chemotherapy were also associated with lower risk of recurrence compared to surgery alone, but the differences did not reach statistical significance [6]. A larger study from Denmark found that the probability of survival without local recurrence was higher when patients with Dukes' B or C rectal cancer received postoperative radiation, compared to surgery alone. The risk of distant metastasis was not influenced by radiation [15]. The Medical Research Council Rectal Cancer Group trial also demonstrated that postoperative radiotherapy reduced the risk of local recurrence with patients with mobile Dukes' stage B or C rectal cancer, without increasing the risk of serious late bowel complications. In this study, radiation did not affect the risk of distant metastasis or overall survival [16]. Finally, the NSABP-R02 protocol found that radiotherapy added to chemotherapy, either 5-FU/LV or 5-FU, semustine, and vincristine, reduced the risk of locoregional recurrence compared to chemotherapy alone in patients with Dukes' B or C rectal cancer [17].

Preoperative Radiotherapy

A number of prospective trials randomizing patients to preoperative radiation and surgery versus surgery alone provided mixed results [14–18]. These studies used variable total radiation doses, fractionation schemas, number of beams, portals, target volumes, radiation, and surgery. In general, only studies that use higher biologically equivalent radiation doses and a higher number of beams proved to reduce local recurrence in patients treated with preoperative radiation compared to surgery alone. The Swedish Rectal Cancer trial demonstrated that short-course preoperative radiation (25 Gy of radiation delivered in 5 equal doses in 5 consecutive days) improved not only local recurrence but also overall survival [7]. However, this study was later criticized because surgery was not standardized and the rate of local recurrence in the control arm was considered high for those years' standards. The Dutch Rectal Cancer trial (CKVO 95-04) was the first to prove that preoperative radiation also reduced the risk of local recurrence rate in patients having optimal surgery according to the principles of total mesorectal excision [13]. The study compared preoperative radiotherapy (5 Gy × 5) followed by quality-controlled TME with TME alone. In this study, the rate of local recurrence in the TME-only arm was substantially lower compared with patient treated with surgery alone in previous trials. Despite the improved surgical technique in both arms, the rate of local recurrence at 5 years was reduced from 10.9 % in the surgery-only group to 5.6 % in the radiotherapy plus surgery group ($p < 0.001$). While no benefit in overall survival was observed for the entire group, the 12-year updated results demonstrated that preoperative short-term radiotherapy significantly improved 10-year survival in patients with stage III disease and negative circumferential margins, and the benefit in terms of local control persisted [19].

Radiosensitizing Agents

Further improvements in local tumor control have been achieved by adding systemic chemotherapy to radiotherapy. Numerous chemotherapeutic agents including fluoropyrimidines (5FU) and capecitabine; irinotecan, oxaliplatin, and antiepidermal growth factor agents; and cetuximab and panitumumab have been tested in the neoadjuvant setting with radiotherapy. With the exception of fluoropyrimidines, however, none have been effectively validated in prospective trials.

Fluoropyrimidines

5-Fluorouracil (5-FU) is the primary agent for radiosensitization in rectal cancer. While its potential to create a state of radiosensitivity was recognized early on, numerous studies eventually led to the understanding that 5-FU's benefit was linked to the schedule of its administration. 5-FU must be present after radiation exposure to establish the radiosensitive state, and for this reason, bolus 5-FU quickly fell out of favor and continuous venous infusion (CVI) 5-FU 225 mg/m^2 daily became the standard [18, 20].

The GITSG proved the overall benefit of combining chemotherapy with postoperative radiation in patients with Dukes' B and C rectal cancer [6]. The North Central Cancer Treatment Group (NCCTG) study compared postoperative radiotherapy with 5-FU administered either as a bolus or as CVI. Patients in the NCCTG trial also received two months of systemic chemotherapy before and after the combined chemotherapy and radiation [21]. This study showed that CVI was associated with a significant decrease in the overall rate of local tumor relapse and distant metastasis, compared to bolus infusion of 5-FU during radiation [21]. Other trials from the Intergroup consortia have shown that CVI 5-FU was associated with lower hematologic toxicity compared to bolus 5-FU [22].

The European Organization for Research and Treatment of Cancer (EORTC) protocol 22921 was developed to assess the effect of adding chemotherapy (CT) to preoperative RT and the value of postoperative chemotherapy in LARC [23]. One thousand and eleven patients were randomized across four arms: (a) preoperative radiotherapy, (b) preoperative radiotherapy plus bolus 5-FU and leucovorin, (c) preoperative radiotherapy followed by postoperative CT, and (d) preoperative radiotherapy and bolus 5-FU and leucovorin followed by postoperative chemotherapy. Five-year local recurrence was significantly lower in all three arms receiving any form of chemotherapy (pre- or postoperative) compared to radiotherapy alone, though

there was no significant improvement in survival. Additional work by the Federation Francophone de la Cancerologie Digestive demonstrated that the addition of 5-FU to RT improves local control but not survival, consistent with the EORTC 22921 trial data [24]. More recently, in a randomized phase III trial, Hofheinz and colleagues were able to show non-inferiority of capecitabine, the oral prodrug of fluorouracil, when compared to 5-FU, providing us a convenient treatment alternative for reliable and motivated patients [25]. The equivalence of capecitabine and 5-FU has also been corroborated with the NSABP-R04 cohort [26].

Oxaliplatin

A number of large phase III trials have evaluated the potential role of oxaliplatin to increase radiosensitivity. The STAR-01 [27], the ACCORD 12/0405-PRODIGE2 [28], and the NSABP-R04 [26] trial each investigated the addition of oxaliplatin to a fluoropyrimidine as radiosensitizing agents. This combination, however, resulted in greater toxicity with no improvement in therapy. Conversely, the CAO/ARO/AIO-04 trial [28] found that the inclusion of oxaliplatin to a 5-FU-based CRT regimen led to a higher pCR rate, with no increase in toxicity [29]. While encouraging, their 5-FU dosing and schedule differed between the control arm and the arm with oxaliplatin, which could have affected the outcomes. At this point, oxaliplatin is not routinely included in the neoadjuvant regimens currently used for rectal cancer.

Irinotecan

This topoisomerase inhibitor has shown significant antitumor activity in metastatic colorectal cancer. While there have been small phase II trials to show that irinotecan may be effective and safe as an adjunct to traditional 5-FU and radiotherapy [30, 31], there has not yet been any trial to show its efficacy over 5-FU and radiotherapy alone.

EGFR Inhibitors

The success and efficacy of anti-EGFR agents like cetuximab and panitumumab in KRAS wild-type metastatic colorectal cancer have brought about a number of studies evaluating its use in the preoperative treatment of LARC. Response rates when EGFR inhibitors are used in the neoadjuvant setting with other agents and radiotherapy have been inconsistent, sometimes positive [32], but mostly equivocal or negative [33, 34]. Some studies have found worse response with their use, which suggests there may be mechanisms of response in tumors to these combined modality treatments that are not yet understood. EGFR inhibitors are not used in the setting of neoadjuvant chemoradiation.

Preoperative Versus Postoperative Radiation

Although there was once great debate on this subject, the preponderance of the evidence supports the use of neoadjuvant radiotherapy versus postoperative adjuvant radiotherapy. The rationale for this approach is logical: neoadjuvant radiotherapy requires less of a dose to achieve the same biologic effect, most likely due to the absence of postoperative scarring and tissue hypoxia in the pelvis. In addition the toxicity, both short term and long term, of neoadjuvant therapy is markedly reduced compared to postoperative radiotherapy, especially when the patient undergoes neorectal reconstruction. Lastly, the proportion of patients who can complete that therapy is markedly improved when radiotherapy is administered in the preoperative period. A small Scandinavian trial comparing preoperative short-course radiation (25.5 Gy in 1 week) for all rectal cancer patients with prolonged postoperative radiation (60 Gy in sever or 8 weeks) for patients with tumors that penetrated into the perirectal fat and/or involved the regional lymph nodes demonstrated that local recurrence was lower after preoperative radiation (13 % vs. 22 %), but survival was similar in both groups. Morbidity was also similar in both groups [35]. The RTOG 94-01 trial aimed to compare preoperative and postoperative CRT but closed after having accrued only 53 of the intended 770 patients. Similarly the National Surgical Adjuvant Breast and Bowel Project (NSABP R-03) also validated the role of neoadjuvant 5-FU-based chemoradiotherapy for LARC. While this study also failed to meet the accrual goal of 900 patients, the analysis of the 267 patients randomized before closure suggested that the preoperative CRT arm had better disease-free survival and probably better overall survival, but similar local recurrence compared to the postoperative arm [36].

The landmark German Rectal Cancer Study (CAO/ARO/AIO-94) compared pre- and postoperative chemoradiotherapy in 823 patients with LARC [37]. The local recurrence rate after 5 years was lower in the preoperative treatment group, 6 % vs. 13 % ($p = 0.006$), while overall survival and the frequency of distant metastases were not significantly different. Importantly, preoperative chemoradiotherapy was associated with a lower risk of grade 3 or 4 toxicities (27 %) compared to postoperative chemoradiation (40 %) [37]. Based on these studies, a commonly employed treatment paradigm for LARC is preoperative 5-FU-based chemoradiotherapy, followed by proctectomy and additional 5-FU-based adjuvant chemotherapy. Specifically, patients receive combined radiation (180 cGy/day/5 days a week for 5 weeks followed by a 540 cGy boost) and chemotherapy (either continuous infusion 5-FU or capecitabine), followed by proctectomy 6–8 weeks later, and postoperative systemic adjuvant chemotherapy, usually mFOLFOX6. In this treatment paradigm, now considered

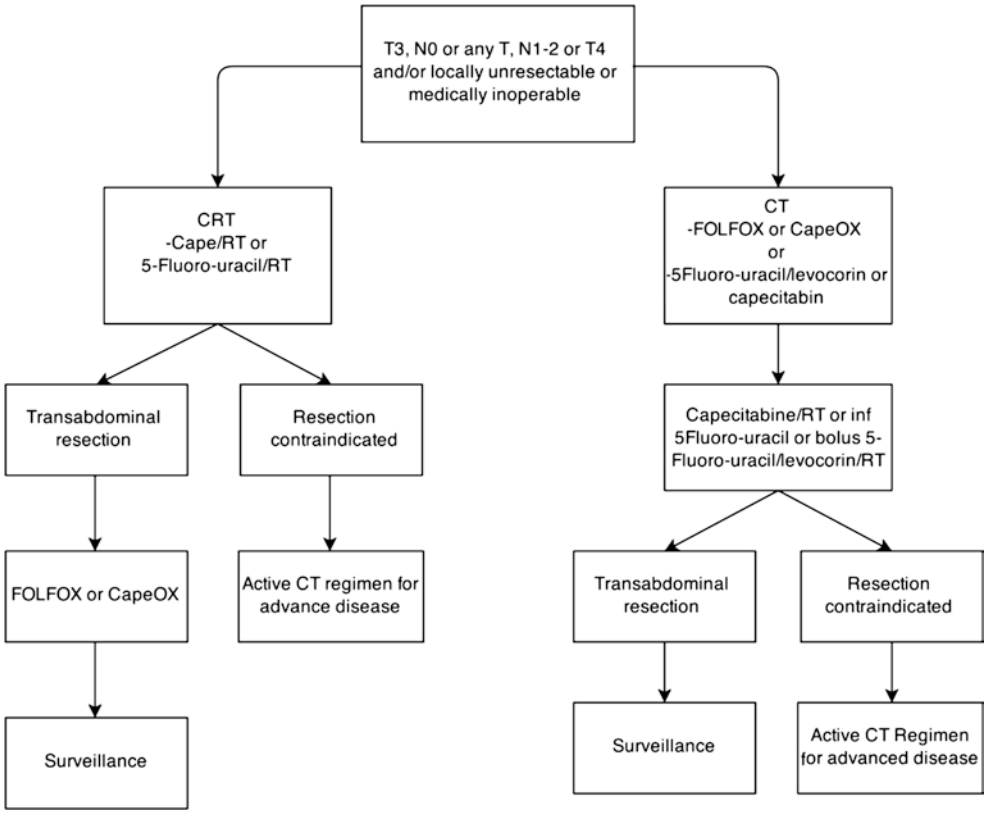

FIGURE 28-1. National Comprehensive Cancer Network guidelines for locally advanced rectal cancer. Permission from JCO/NCCN (*Cape* capecitabine, *CapeOx* capecitabine plus oxaliplatin, *CRT* chemoradiation, *CT* chemotherapy, *FLOX* fluorouracil, leucovorin, and oxaliplatin, *FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil, *inf.* infusional, *LR* local recurrence, *LV* leucovorin, *MRF* mesorectal fascia, *RT* radiotherapy, *TME* total mesorectal excision). With permission from Neoadjuvant chemoradiation therapy and pathological complete response in rectal cancer. Gastroenterology Report. Gastroenterol Rep 2015 doi: 10.1093/gastro/gov039. http://gastro.oxfordjournals.org/content/early/2015/08/19/gastro.gov039.full. Copyright © 2015 Oxford University Press and Digestive Science Publishing Co. Limited.

standard practice in the United States (Figure 28-1), imaging has become increasingly important for preoperative tumor staging and patient selection.

Short- Versus Long-Course Preoperative Radiotherapy

The effectiveness of radiation depends on the balance between the cytotoxicity against cancer and the preservation of adjacent normal tissues. There is now evidence of a dose-response relationship with radiotherapy, with an improved cytotoxic effect with higher total doses of radiation. However, the total dose of radiation depends on the dose per fraction and the number of fractions, the dose-fractionation schedule. But the dose per fraction and the number of fractions used in clinical practice vary widely. To compare different dose fractionation schedules, radiation therapists have introduced the concept of biologically equivalent doses. The most common dose-fractionation schedules used in rectal cancer, 1.8–2 Gy per day, 5 days per week for 5 weeks (usually in combination with a fluoropyrimidine) and 5 Gy as day for 5 consecutive days, are considered biologically equivalent. The advantages and disadvantages of each one of these regimens have been the subject of a heated debate. Proponents of long-course chemoradiotherapy point to a greater tumor response, although this may be an artifact of the greater time delay prior to proctectomy typically utilized after long-course chemoradiotherapy (typically 6–8 weeks) as compared to after short-course radiotherapy (typically 1 week). Those in favor of short-course radiation argue that improved patient convenience, lower cost, reduced toxicity in the neoadjuvant treatment period, and faster time to effective systemic chemotherapy are important advantages. Two trials have compared these two approaches directly.

Bujko and colleagues prospectively compared the two regimens, randomizing 316 patients with clinical T3 or T4 disease to either neoadjuvant long-course chemoradiotherapy or neoadjuvant short-course radiotherapy, and found that long-course chemoradiotherapy was associated with a significantly decreased incidence of positive radial margins (4.4 % vs. 12.9 %, $p=0.017$) and a higher rate of pCR (0.7 % vs. 16.1 %), but this did not carry over into a significant difference in pelvic control, disease-free survival, or overall survival [10]. Moreover, they reported greater radiation toxicity in the long-course chemoradiotherapy group and poorer compliance to treatment schedule. Their conclusion was that short-course radiotherapy was a viable alternative to long-course chemoradiotherapy with neither holding a long-term oncologic advantage, but with short-course radiotherapy potentially benefiting from lower cost and lower morbidity associated with its use. More recently, theTrans Tasman Radiation Oncology Group 01.04 randomized 326

patients with ERUS- or MRI-staged T3, N0–2, M0 tumors to short-course radiotherapy and surgery followed by 6 months of adjuvant chemotherapy or chemoradiotherapy and surgery followed by 4 months of adjuvant chemotherapy [11]. Their study was powered to detect a 10 % difference in local recurrence at 3 years, with a 5 % level of significance. Similar to the work of Bujko et al., the Trans Tasman trial found no difference in pelvic control, disease-free survival, and overall survival between the groups. Patient imbalances between groups have been called to attention, with fewer patients with low rectal cancers in chemoradiotherapy than the short-course radiotherapy arms (which would bias the results in favor of the chemoradiotherapy group) and varying rates of APR. The quality of surgery and accuracy of MRI staging have also been criticized [38, 39]. Nevertheless, two prospective randomized trials have demonstrated no obvious oncologic differences between neoadjuvant long-course chemoradiotherapy and neoadjuvant short-course radiotherapy.

The short-course and long-course divide has remained somewhat static across national boundaries, with a Western preference for long-course chemoradiotherapy and a majority of European countries favoring short-course radiotherapy. It is puzzling that, except for a few expert centers, short-course radiotherapy has not been embraced by US physicians. One could argue that it is the best-studied neoadjuvant radiotherapy regimen, with demonstrated efficacy in prospective randomized trials of neoadjuvant radiotherapy versus surgery alone, and shortens the time to administration of full-dose adjuvant cytotoxic chemotherapy.

Because of a current trend exploring the incorporation of therapies traditionally reserved for the adjuvant period into the neoadjuvant regimen, combinations of either short-course radiotherapy or long-course chemoradiotherapy with systemic therapies are being explored and gaining greater traction. Therefore, it may never be clearly determined whether short-course or long-course RT is more effective as independent modalities.

Impact of Pelvic Radiotherapy on Quality of Life

Another advantage of preoperative radiotherapy is the potential ability to downstage tumors and to increase the potential for sphincter-sparing surgery, which can improve long-term quality of life for patients with low-lying rectal cancers [37]. The issue of sphincter salvage, however, is complicated. As one might imagine, the assessment of whether a restorative proctectomy could possibly be performed based on initial evaluation of a patient is somewhat subjective. In addition, given that radiotherapy does not kill tumor in a wave front, and that multiple studies have demonstrated residual tumor scattered throughout the bed of the initial volume of tissue involved with the tumor, many surgeons would argue that changing the operation based on the clinically observed effect of radiotherapy is potentially dangerous. However, by improving the chances of an R0 resection and decreasing the rates of local recurrence, which can be associated with significant morbidity, radiotherapy can improve long-term quality of life. Nevertheless, pelvic radiotherapy remains associated with significant short- and long-term side effects. Overall short-term toxicity has been reported in as many as 50 % of patients [40]. Long-term side effects of pelvic radiotherapy include fibrosis and autonomic nerve injury, which can lead to bowel and bladder dysfunction, sexual dysfunction, and infertility due to hormonal effects and uterine incompetence. Moreover, because the pelvis is an active site of bone marrow function, patients who undergo pelvic irradiation can suffer from diminished hematopoiesis.

Adjuvant Systemic Chemotherapy in Patients Treated with Chemoradiotherapy and Proctectomy

Although prevention of local recurrences is important for patients' quality of life, most patients with rectal cancer succumb to metastatic disease. Consequently, similar to patients with stage III colon cancer, patients with LARC patients treated with neoadjuvant chemoradiotherapy and proctectomy are considered for postoperative adjuvant chemotherapy independent of the histologic tumor stage in the proctectomy specimen [41]. Patients with clinical stage II and III rectal cancer treated with preoperative chemoradiotherapy and proctectomy usually receive 5-FU or capecitabine plus oxaliplatin-based adjuvant chemotherapy [41]. While the use of postoperative adjuvant chemotherapy in rectal cancer is not supported unequivocally by a prospective randomized trial, a recent meta-analysis of 21 randomized controlled trials concluded that postoperative 5-FU-based chemotherapy is effective in patients with LARC [42].

In spite of these recommendations, up to 27 % of eligible LARC patients never start adjuvant chemotherapy and less than 50 % [43] receive the full prescribed treatment without interruptions or delay [23, 29] due to postoperative complications, slow recovery, interference with closure of their temporary ileostomy [44], or simply treatment refusal [45]. A systematic review of ten studies including more than 15,000 patients evaluated the effect of timing on the efficacy of postoperative adjuvant chemotherapy and demonstrated that each 4-week delay in treatment correlated with a 14 % decrease in OS [46].

It is interesting to note that, despite the common practice of administering chemotherapy, a recent meta-analysis of adjuvant chemotherapy in LARC did not demonstrate a survival benefit. In total 1196 patients with stage II or III disease and R0 resection were evaluated; 598 were observed while 598

received adjuvant chemotherapy [47]. However, of the four studies included in the analysis, only one used oxaliplatin in combination with fluorouracil, the CHRONICLE trial which contributed only 75 patients to this analysis [48]. Moreover, completion of planned chemotherapy was low in all of the studies (43–76 %). This low adherence could certainly have affected the results [47].

Due to the low rate of completion of planned adjuvant therapy, splitting adjuvant chemotherapy and delivering a limited number of cycles pre-chemoradiotherapy, then delivering the remaining cycles postsurgery, has been proposed to increase tumor response in LARC patients. A number of randomized phase II trials have reported mixed results, without clear survival advantage for the split neoadjuvant or the postoperative regimen [48–52].

Another potential approach is to deliver all chemotherapy upfront. This neoadjuvant chemotherapy has several potential advantages compared to the standard adjuvant chemotherapy; it theoretically treats occult micrometastasis several months earlier and increases treatment compliance, potentially enhancing the efficacy of chemotherapy and ultimately improving survival [53, 54]. Other benefits of neoadjuvant chemotherapy include increased response of the primary tumor, early identification of nonresponders, and earlier removal of the loop ileostomy. A recent study at Memorial Sloan Kettering Cancer Center (MSKCC) investigated the safety and efficacy of FOLFOX before CRT, demonstrating excellent treatment compliance and no evidence of serious adverse effects requiring treatment delay. All patients undergoing proctectomy had an R0 resection, and nearly half had a tumor response greater than 90 % including 30 % who had either a pCR or a clinical complete response (cCR) [55]. Induction chemotherapy before chemoradiation and proctectomy is now considered as a valid alternative to the more widely accepted neoadjuvant chemoradiation, proctectomy, and postoperative systemic chemotherapy (Figure 28-1).

Chemotherapy can also be delivered as consolidation (after chemoradiotherapy completion and before surgery). The Timing of Rectal Cancer Response to Chemoradiation Trial, which completed accrual in 2012, showed that delivering 2, 4, or 6 cycles of FOLFOX after chemoradiotherapy in LARC patients increased the pCR rates up to 25 %, 30 %, and 38 %, respectively, compared to CRT alone (18 %), without any associated increase in adverse events or surgical complications [56]. Eighty percent of patients received consolidation chemotherapy without interruption. These studies suggest that delivering systemic chemotherapy in the neoadjuvant setting, both before or after chemoradiotherapy, is well tolerated and has potential advantages for the patient. Although solid data from large prospective studies are still lacking, in the most recent edition of the NCCN guidelines, neoadjuvant chemotherapy is contemplated as an option for the treatment of LARC patients. However, none of these studies have reported long-term oncologic outcomes.

Setting the Right Limits

Chemoradiotherapy has clearly proved itself useful at improving local tumor control in patients with LARC. We find that the weight of evidence is also demonstrating that systemic chemotherapy—when applied in the neoadjuvant setting—is able to similarly control tumor progression, possibly acting on micrometastatic disease to improve distant control. But while the benefits of these intensive neoadjuvant regimens are alluring, they have also sparked a heated debate about whether all patients require such intensive treatment. The oncologic success in treating LARC has been achieved at the cost of significant morbidity and compromised quality of life [40]. The task before us is to develop treatment approaches that maximize oncological outcome while preserving quality of life by minimizing morbidity associated with this intense multimodality approach [57]. Do all patients with LARC really require chemoradiotherapy, chemotherapy, and proctectomy? The necessity of this intense multimodality approach is called into question.

The European Approach

In a number of European countries, the "right limits" have been framed around MRI-based measures of tumor aggressiveness. A risk stratification system that covers all rectal cancers and that incorporates the proximity of the primary rectal cancer to the mesorectal fascia, the depth of tumor invasion, the presence of metastatic lymph nodes, and the presence of venous invasion are used to classify LARC into "the good," "the bad," and "the ugly" [58, 59]. For the low-risk, "good" tumors, proctectomy alone is recommended; for intermediate-risk "bad" tumors, the recommendation is short-course radiotherapy followed by proctectomy; and for high-risk "ugly" tumors, chemoradiotherapy followed by proctectomy is recommended (Table 28-1). These MRI-based risk stratification schemas have been incorporated into clinical practice guidelines and clinical trial design (e.g., Expert-C and RAPIDO). However, the treatment approach guided by MRI risk categorization is based on prospective observational studies conducted in institutions with significant expertise in rectal cancer and has not been tested in prospective randomized trials.

Selected Adjuvant Systemic Chemotherapy

Many LARC patients experience variable degrees of response to chemoradiotherapy, and tumor response is now one of the most important prognosticators in LARC patients [2, 57]. The need for adjuvant chemotherapy in patients with a complete or near-complete response after chemoradiotherapy has been questioned [60–62]. Recent work from a multi-institutional, retrospective analysis of 3133 patients shows that the benefit of adjuvant therapy differs between LARC subgroups. For example, patients with ypT1-2 or ypT3-4 tumors benefitted

Table 28-1. European/Scandinavian model of stratification for patients with locally advanced rectal cancer based on magnetic resonance imaging and subsequent treatment decisions

Risk	Treatment
Low risk	
• T1–T3 (<5 mm) mid-/upper rectum • T1–T3 (superficial) lower rectum • N0 • Extramural vascular invasion: no mesorectal fascia clear • Risk of local recurrence <10%	Total mesorectal incision (TME)
Intermediate risk	
T3 (<5 mm)	• Preoperative short course radiation
T4 (posterior vaginal wall only), or N1/2, or Extramural vascular invasion: yes Mesorectal fascia clear (<1 mm) Risk of local recurrence: 10–20 %	• Total mesorectal excision • Adjuvant chemotherapy
High risk	
T4 (other than posterior vaginal wall)	• Preoperative chemoradiation
N01/2 Mesorectal fascia involved Risk of local recurrence >20 %	• Total mesorectal excision • Adjuvant chemotherapy

Modified from Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. J Clin Oncol 2005

the most from adjuvant therapy compared with ypT0N0 patients [63]. Some centers now use postoperative chemotherapy selectively based on tumor response to chemoradiotherapy. In the recently published ADORE phase II trial, which examined use of selective adjuvant chemotherapy, LARC patients with ypT3-4N0 or ypTanyN1-2 tumors after fluoropyrimidine-based chemoradiotherapy were randomized to adjuvant chemotherapy with either 4 cycles of 5-FU and LV or 8 cycles of FOLFOX. The administration of FOLFOX after surgery was associated with prolonged progression-free survival in stage III patients but not in stage II patients. Additionally, FOLFOX was associated with a prolonged overall survival for both stage II/III rectal cancer patients [64]. Identification of those patients who will most likely to derive benefit from adjuvant treatment will be better informed by carefully conducted correlative studies that more accurately delineate molecular, pathologic, and clinical markers of resistance.

Chemotherapy Only to Improve Local Tumor Control

The risk of local pelvic failure in LARC depends on tumor stage, but also on the distance of the tumor from the anal verge and the proximity of the tumor from the mesorectal fascia [13, 65]. Upper rectal tumors away from the mesorectal fascia have a low risk of local recurrence when treated with proctectomy. The added benefit of radiotherapy in these patients has been questioned [40, 66, 67]. A growing body of evidence suggests that radiotherapy could be safely avoided in patients with intermediate-risk rectal cancer (e.g., rectal cancers located between 5 and 12 cm from the anal verge that do not threaten the mesorectal fascia) on MRI [68, 69]. In a pilot phase II trial conducted at MSKCC, 32 patients with resectable, clinically staged II–III rectal cancer were treated with preoperative FOLFOX/anti-VEGF and selective chemoradiotherapy, based on tumor response. The 30 patients who completed preoperative chemotherapy had tumor regression and underwent proctectomy without preoperative chemoradiotherapy. Eight (27 %) had pathologic complete responses. No local recurrences were noted at 4 years, and an 84 % disease-free survival was achieved [70]. Given these data, a large multicenter phase II/III study is currently accruing patients. In the CALGB PROSPECT Study (Preoperative Radiation Or Selective Preoperative Evaluation of Chemotherapy and TME) [71], patients are randomized to either the standard arm (chemoradiotherapy, surgery, and adjuvant FOLFOX chemotherapy) or the selective arm with FOLFOX×6 cycles, evaluation of response followed by surgery or standard therapy with chemoradiotherapy if the reduction in the primary tumor is <20 % (Figure 28-2). Eligible patients must have biopsy-proven adenocarcinoma with the primary tumor located 5–12 cm from the anal verge. They must be candidates for sphincter-sparing surgery. The primary outcomes of the phase II component are R0 resection rate and time to local recurrence. The primary endpoints of the phase III components are time to local recurrence and disease-free survival. The selective chemoradiation arm will be favored if either the disease-free survival is superior compared to the standard arm or if it is non-inferior to the standard arm for both disease-free survival and local recurrence. In addition to this study, there is currently an ongoing study, the GEMCAD study, on induction chemotherapy with or without chemoradiation in intermediate-risk rectal cancer defined by MRI. This study was presented in abstract form in the 2010 annual ASCO meeting; the final data have not yet been presented [72]. In this study which is no longer accruing patients, patients with T3 or T1–2N1 tumors based on MRI were treated with bevacizumab and CapeOX (capecitabine and oxaliplatin) for three cycles followed by repeat MRI evaluation. Those patients with response went on to proctectomy, while nonresponders received standard chemoradiotherapy. A third study is a phase II randomized study of neoadjuvant FOLFOX/bevacizumab versus FOLFOXIRI/bevacizumab in patients with high-risk rectal cancer as defined by MRI. This study is not yet open to accrual but will also add insight into the response of the primary rectal tumor to chemotherapy alone [73]. These studies will provide important insight into the potential for a more individualized treatment approach through selective use of radiation in LARC.

Selective Nonoperative Management

Proctectomy is the cornerstone of the treatment algorithm for LARC patients. However, up to 33 % of LARC patients treated with neoadjuvant chemoradiotherapy exhibit

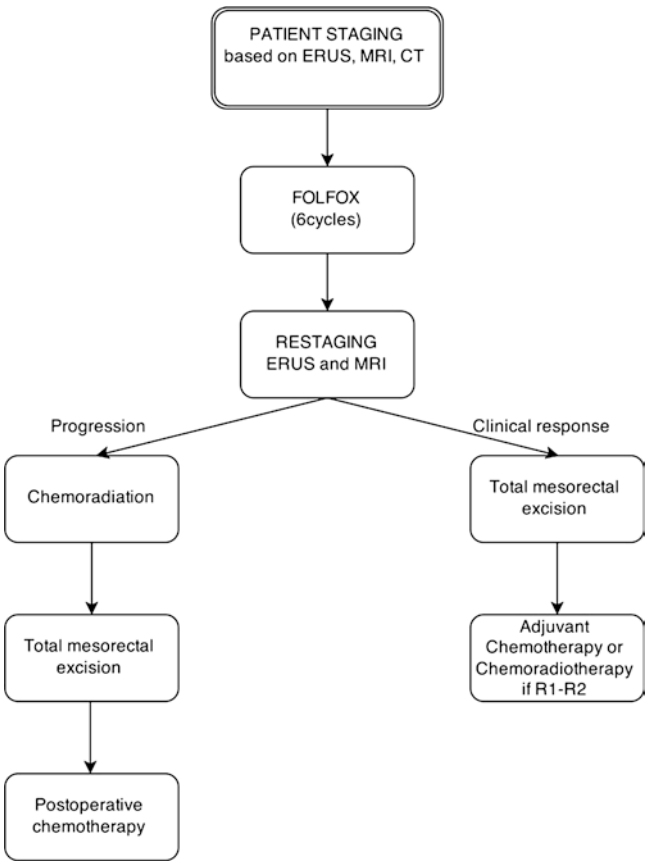

FIGURE 28-2. PROSPECT (Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients with Locally Advanced Cancer Undergoing Surgery) trial schema. A phase II/III randomized study designed to evaluate the impact of selective use of radiotherapy compared with nonselective use of chemoradiation for patients with locally advanced rectal cancer. (*FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin, *LAR* low anterior resection, *FUCMT* fluorouracil or capecitabine plus radiotherapy, *TME* total mesorectal excision.) With permission from Neoadjuvant chemoradiation therapy and pathological complete response in rectal cancer. Gastroenterology Report. Gastroenterol Rep 2015 doi: 10.1093/gastro/gov039. http://gastro.oxfordjournals.org/content/early/2015/08/19/gastro.gov039.full. Copyright © 2015 Oxford University Press and Digestive Science Publishing Co. Limited.

a pathologic complete response (pCR) at the time of surgical resection [74, 75]. Patients with a pCR have improved oncologic outcomes with local recurrence rates of less than 1 % and a 5-year survival rate of over 90 % [3, 76], leading us to question the added benefit of proctectomy for these patients. The potential gains of avoiding proctectomy—reduced morbidity, improvement in quality of life, and potential reduction of health care expenses—could be significant. The current challenge lies in accurately identifying which patients have achieved a pCR and could safely avoid proctectomy [77]. Although cCR does not always correlate with pCR, and current imaging modalities cannot distinguish with certainty tumor remnants from tissue fibrosis [78, 79], a number of institutions have reported their experience with the selective use of an organ-preserving or NOM approach in patients with a complete clinical response after chemoradiotherapy (Table 28-2) [80–84]. The largest experience with the NOM approach to rectal cancer comes from Habr-Gama's group in Sao Paulo, Brazil [80–82]. Patients with persistent tumor underwent proctectomy; those with a complete clinical response were enrolled in a strict follow-up protocol. Patients with evidence of tumor relapse were directed to surgery, while patients with a sustained complete clinical response after 1 year continued surveillance every 3 months for an additional year and every 6 months thereafter. Twenty-seven percent of rectal cancer patients treated according to this protocol had a sustained complete clinical response and were spared from proctectomy. Of the patients who survived 1 year following treatment and did not show any evidence of tumor progression, local recurrence during follow-up developed in 10 %, but all had proctectomy with curative intent. The oncologic results in this NOM group were equivalent to those of patients who had a pathologic complete response after proctectomy. However, the authors did not evaluate patients on an intention-to-treat basis. By excluding those patients who failed treatment during the first year, results were heavily biased in favor of the NOM group. A group from Maastricht University in the Netherlands reported their NOM experience in 21 patients with complete clinical response as determined by clinical exam, MRI, and endoscopic biopsy among 192 patients treated with chemoradiotherapy between 2004 and 2010 [83]. After a mean follow-up of 25 ± 19 months, 1 patient developed LR, but was able to undergo curative salvage surgery. The other 20 patients are alive without disease. Outcomes in patients with complete clinical response treated according to the NOM protocol were similar to outcomes of patients with a pathologic complete response after proctectomy. At MSKCC, rectal cancer patients with a complete clinical response have been managed under an NOM strategy since 2006. Of the 32 patients starting treatment before 2010 who were followed for a median of 23 months, 6 patients developed relapse, and all underwent salvage surgery with curative intent; additionally, 3 of these patients also developed distant metastases [84]. The combined experience of these series suggests that NOM may be an alternative approach to proctectomy in highly select patients with distal rectal cancer who achieve a complete clinical response to neoadjuvant therapy (Table 28-2). However, the safety and efficacy of the NOM approach outside of centers specializing in the treatment of rectal cancer is controversial. It is now clear that even with strict complete clinical response definitions, some patients will later develop local recurrence, emphasizing the importance of close surveillance, because the success of this approach relies on the early diagnosis of recurrences and timely salvage therapy. In addition, the risk of distant metastases in patients with an apparent complete clinical response that develop local tumor regrowth and subsequent outcomes is unknown. Therefore, at the present time, the NOM of rectal cancer should be considered experimental.

The design of large, prospective randomized trials investigating the efficacy of the NOM approach is challenging,

TABLE 28-2. Summary of the most representative series, nonoperative vs. operative management of LARC after CRT

Series	# cCRs	%	Mean interval to LR	# Patients	OS				DFS			
					NOM		Operative arm		NOM		Operative arm	
					Survival	%	Survival	%	Survival	%	Survival	%
Habr-Gama et al. [80]	71	27	60	2	5 years	100	5 years	88	5 years	92	5 years	83
Habr-Gama et al. [81]	90	49	17	28	5 years	91	NA		5 years	68	NA	
Maas et al. [83]	21	11	22	1	2 years	100	2 years	91	2 years	89	2 years	93
Smith et al. [84]	32	NA	11	6	2 years	97	2 years	88	2 years	100	2 years	88
Dalton [90]	12	24	24[a]	6	26 months	100	26 months	100	26 months	100	26 months	100[b]

cCR clinical complete response, *CRT* chemoradiotherapy, *DFS* disease-free survival, *LARC* locally advanced rectal cancer, *LR* local recurrence, *NA* not available, *NOM* nonoperative management, *OS* overall survival, *RT* radiotherapy, *pCR* pathological complete response

[a]Mean time to surgery

[b]All six with pCR

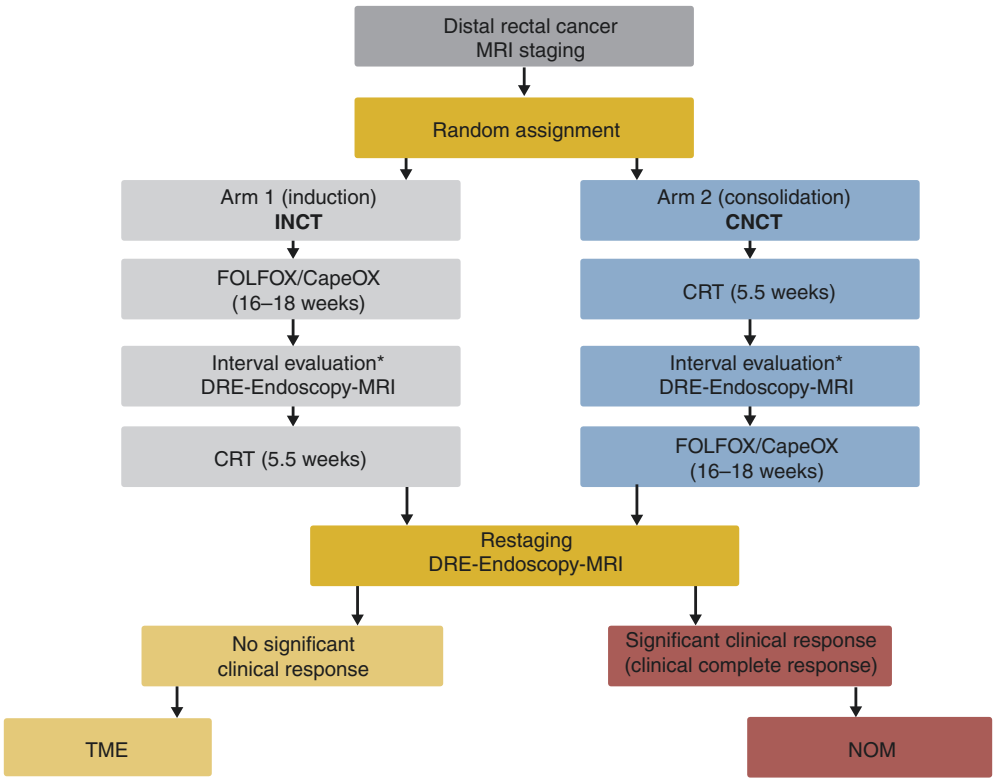

FIGURE 28-3. Memorial Sloan Kettering Cancer Center phase II trial schema that is underway to test the feasibility of incorporating a nonoperative management (NOM) to the multimodality treatment of rectal cancer in a multi-institutional setting. (*Cape* capecitabine, *CapeOx* capecitabine plus oxaliplatin, *CNCT* chemotherapy plus consolidation CRT, *CRT* chemoradiation, *DRE* digital rectal examination, *FOLFOX* infusional fluorouracil, leucovorin, and oxaliplatin, *FU* fluorouracil, *FUCMT* fluorouracil or capecitabine plus radiotherapy, *INCT* induction chemotherapy, *MRI* magnetic resonance imaging, *RT* radiotherapy, *TME* total mesorectal excision.) Courtesy of Julio Garcia-Aguilar.

given the relatively small proportion of patients with a complete clinical response to standard neoadjuvant chemoradiotherapy and the disparity of the treatment arms—observation versus proctectomy. However, a number of prospective observational studies [85–87] and phase II trials, including our own (Figure 28-3), are underway to test the feasibility of incorporating an NOM approach to the multimodality treatment of rectal cancer in a multi-institutional setting [88, 89].

Summary

Decades of clinical research have resulted in a variety of multimodality treatment paradigms for rectal cancer patients providing unprecedented local tumor control and patient survival. Although this represents a significant achievement in oncologic outcome, multimodality therapy can be associated with significant morbidity and long-term sequelae that can impair quality of life permanently. Identification of patients at

different risk levels for tumor recurrence and survival based on baseline tumor characteristics and response or resistance to therapy should enable us to tailor treatments accordingly and in certain cases omit radiation or surgery to decrease morbidity without compromising outcomes.

References

1. De Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Ann Surg Oncol. 2011;18:1590–8.
2. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11:835–44.
3. 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. 2012;99:918–28.
4. Janeway HH. Treatment of cancer, particularly of the tongue, tonsil and rectum, by buried emanation. Read at the Third Annual Meeting of the American Radium Society. 1919 June 5; Atlantic City, NJ.
5. Binkley GE. Radiation in the treatment of cancer of the rectum. Ann Surg. 1929;90(6):1000–14.
6. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med. 1985;312:1465–72.
7. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997;336(14):980–7. Erratum in: N Engl J Med. 1997;336(21): 1539.
8. Gerard A, Buyse M, Nodingler B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg. 1988;208(5):606–14.
9. Adjuvant therapy for patients with colon and rectum cancer. Consens Statement. 1990;8(4):1–25.
10. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93:1215–23.
11. Ngan SY, Burmeister B, Fisher RJ, 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;30:3827–33.
12. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1:1479–82.
13. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638–46.
14. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet. 2001;358:1291–304.
15. Balslev I, Pedersen M, Teglbjaerg PS, Hanberg-Soerensen F, Bone J, Jacobsen NO, Overgaard J, Sell A, Bertelsen K, Hage E, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. Cancer. 1986;58(1):22–8.
16. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. Lancet. 1996;348(9042): 1610–4.
17. Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, Wexler M, Prager D, Cruz Jr AB, Gordon PH, Petrelli NJ, Deutsch M, Mamounas E, Wickerham DL, Fisher ER, Rockette H, Fisher B. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst. 2000;92(5):388–96.
18. Cammà C, Giunta M, Fiorica F, et al. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. JAMA. 2000;284:1008–15.
19. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, Rutten HJ, Påhlman L, Glimelius B, van de Velde CJ, Dutch Colorectal Cancer Group. 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.
20. Byfield JE. 5-Fluorouracil radiation sensitization—a brief review. Invest New Drugs. 1989;7:111–6.
21. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331:502–7.
22. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol. 2006;24:3542–7.
23. Bosset J-F, Calais G, Mineur L, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. J Clin Oncol. 2005;23:5620–7.
24. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24:4620–5.
25. Hofheinz R-D, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13:579–88.
26. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, Pitot HC, Shields AF, Landry JC, Ryan DP, Parda DS, Mohiuddin M, Arora A, Evans LS, Bahary N, Soori GS, Eakle J, Robertson JM, Moore Jr DF, Mullane MR, Marchello BT, Ward PJ, Wozniak TF, Roh MS, Yothers G, Wolmark N. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol. 2014;32(18):1927–34.
27. Aschele C, Cionini L, Lonardi S, 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;29:2773–80.

28. Gérard J-P, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010;28:1638–44.
29. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012;13:679–87.
30. Navarro M, Dotor E, Rivera F, et al. A phase II study of preoperative radiotherapy and concomitant weekly irinotecan in combination with protracted venous infusion 5-fluorouracil, for resectable locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2006;66(1):201–5.
31. Willeke F, Horisberger K, Kraus-Tiefenbacher U, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer. 2007; 96(6):912–7.
32. Velenik V, Ocvirk J, Oblak I, et al. A phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer. Eur J Surg Oncol. 2010;36(3):244–50. doi:10.1016/j.ejso.2009.12.002.
33. Horisberger K, Treschl A, Mai S, 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. doi:10.1016/j.ijrobp.2008.10.014.
34. Dewdney A, Cunningham D, Tabernero J, 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. doi:10.1200/JCO.2011.39.6036.
35. Pahlman L, Glimelius B. Pre- or postoperative radiation in rectal and rectosigmoid carcinoma. Ann Surg. 1990;21:187–94.
36. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, Kahlenberg MS, Baez-Diaz L, Ursiny CS, Petrelli NJ, Wolmark N. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124–30.
37. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
38. Tan D, Glynne-Jones R. But some neoadjuvant schedules are more equal than others. J Clin Oncol. 2013;31:1799–800.
39. Bujko K. Short-course preoperative radiotherapy for low rectal cancer. J Clin Oncol. 2013;31:1799.
40. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J Clin Oncol. 2005;23:6199–206.
41. Benson AB, Bekaii-Saab T, Chan E, et al. Rectal cancer [Internet]. J Natl Compr Canc Netw. 2012;10:1528–64. http://www.ncbi.nlm.nih.gov/pubmed/23221790. Accessed 25 Oct 2014.
42. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane database Syst Rev. 2012;3, CD004078. http://www.ncbi.nlm.nih.gov/pubmed/22419291. Accessed 6 Nov 2014.
43. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, Bardet E, Beny A, Ollier JC, Bolla M, Marchal D, Van Laethem JL, Klein V, Giralt J, Clavère P, Glanzmann C, Cellier P, Collette L, EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. 2014;15(2): 184–90.
44. Hayden DM, Pinzon MC, Francescatti AB, et al. Hospital readmission for fluid and electrolyte abnormalities following ileostomy construction: preventable or unpredictable? J Gastrointest Surg. 2013;17:298–303. http://www.ncbi.nlm.nih.gov/pubmed/23192425. Accessed 10 Sep 2014.
45. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with Neoadjuvant therapy, LARC: a national comprehensive cancer network analysis. J Clin Oncol. 2013;31:30–8. http://www.ncbi.nlm.nih.gov/pubmed/23169502. Accessed 21 Oct 2014.
46. Biagi JJ, Raphael MJ, Mackillop W, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305:2335–42. http://www.ncbi.nlm.nih.gov/pubmed/21642686. Accessed 25 Oct 2014.
47. 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. 2015;16:200–7.
48. 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. 2014;25:1356–62.
49. Calvo FA, Serrano FJ, Diaz-González JA, et al. Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol. 2006;17:1103–10. http://www.ncbi.nlm.nih.gov/pubmed/16670204. Accessed 22 Sep 2014.
50. Chau I, Brown G, Cunningham D, 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;24:668–74. http://www.ncbi.nlm.nih.gov/pubmed/16446339. Accessed 22 Sep 2014.
51. Fernández-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, l. J Clin Oncol. 2010;28:859–65. http://www.ncbi.nlm.nih.gov/pubmed/20065174. Accessed 22 Sep 2014.
52. Maréchal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol. 2012;23:1525–30. http://www.ncbi.nlm.nih.gov/pubmed/22039087. Accessed 6 Oct 2014.
53. Schou JV, Larsen FO, Rasch L, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol. 2012;23:2627–33. http://

www.ncbi.nlm.nih.gov/pubmed/22473488. Accessed 4 Sep 2014.
54. Glynne-Jones R, Grainger J, Harrison M, et al. Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: should we be more cautious? Br J Cancer. 2006;94:363–71. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2361136&tool=pmcentrez&rendertype=abstract. Accessed 21 Oct 2014.
55. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw. 2014;12(4):513–9.
56. 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. 2015;16(8):957–66. doi:10.1016/S1470-2045(15)00004-2.
57. Glynne-Jones R, Harrison M, Hughes R. Challenges in the neoadjuvant treatment of rectal cancer: balancing the risk of recurrence and quality of life. Cancer Radiother. 2013;17:675–85. http://www.ncbi.nlm.nih.gov/pubmed/24183502. Accessed 5 Sep 2014.
58. Glimelius B, Tiret E, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24:vi81–8.
59. Smith N, Brown G. Preoperative staging of rectal cancer. Acta Oncol. 2008;47:20–31.
60. Chang GJ, Park IJ, Eng C, et al. Exploratory analysis of adjuvant chemotherapy benefits after preoperative chemoradiotherapy and radical resection for rectal cancer. ASCO Meet Abstr. 2012;30:3556. http://hwmaint.meeting.ascopubs.org.proxy.library.vanderbilt.edu/cgi/content/abstract/30/15_suppl/3556. Accessed 7 Nov 2014.
61. Fietkau R, Barten M, Klautke G, et al. Postoperative chemotherapy may not be necessary for patients with ypN0-category after neoadjuvant chemoradiotherapy of rectal cancer. Dis Colon Rectum. 2006;49:1284–92. http://www.ncbi.nlm.nih.gov/pubmed/16758130. Accessed 7 Nov 2014.
62. Nelson VM, Benson AB. Pathological complete response after neoadjuvant therapy for rectal cancer and the role of adjuvant therapy. Curr Oncol Rep. 2013;15:152–61. http://www.ncbi.nlm.nih.gov/pubmed/23381584. Accessed 19 Nov 2014.
63. Maas M, Nelemans PJ, Valentini V, et al. Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection: a pooled analysis of 3,313 patients. Int J Cancer. 2015;137(1):212–20. doi:10.1002/ijc.29355.
64. Hong YS, Nam B-H, Kim K-P, 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. 2014;15:1245–53. http://www.ncbi.nlm.nih.gov/pubmed/25201358. Accessed 12 Sep 2014.
65. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg. 2011;253:711–9. http://www.ncbi.nlm.nih.gov/pubmed/21475011. Accessed 27 Oct 2014.
66. Birgisson H, Påhlman L, Gunnarsson U, et al. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol. 2005;23:8697–705. http://www.ncbi.nlm.nih.gov/pubmed/16314629. Accessed 27 Oct 2014.
67. Joye I, Haustermans K. Early and late toxicity of radiotherapy for rectal cancer. Recent Results Cancer Res. 2014;203:189–201. http://www.ncbi.nlm.nih.gov/pubmed/25103006. Accessed 7 Nov 2014.
68. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol. 2004;22:1785–96. http://www.ncbi.nlm.nih.gov/pubmed/15067027. Accessed 13 Oct 2014.
69. Schrag D. Evolving role of neoadjuvant therapy in rectal cancer. Curr Treat Options Oncol. 2013;14:350–64. http://www.ncbi.nlm.nih.gov/pubmed/23828092. Accessed 13 Oct 2014.
70. 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. 2014;32:513–8. http://www.ncbi.nlm.nih.gov/pubmed/24419115. Accessed 4 Sep 2014.
71. Alliance for clinical trials in oncology: PROSPECT Trial. http://clinicaltrials.gov/sho/NCT01515787
72. Fernandez-Martos C, Safont M, Feliu J, et al. Induction chemotherapy with or without chemoradiation in intermediate-risk rectal cancer patients defined by magnetic resonance imaging (MRI): a GEMCAD study. J Clin Oncol (Meeting Abstracts). 2010;28:15. Suppl TPS 196.
73. Bevacizumab And Combination Chemotherapy in Rectal Cancer Until Surgery (BACCHUS). www.clinicaltrials.gov. Accessed 9 Sep 2015.
74. 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. 1999;17:2396. http://www.ncbi.nlm.nih.gov/pubmed/10561302. Accessed 9 Nov 2014.
75. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol. 2012;30:1770–6. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3383178&tool=pmcentrez&rendertype=abstract. Accessed 6 Nov 2014.
76. Zorcolo L, Rosman AS, Restivo A, et al. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. Ann Surg Oncol. 2012;19(9):2822–32. doi:10.1245/s10434-011-2209-y.
77. Guillem JG, Chessin DB, Shia J, et al. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. J Clin Oncol. 2005;23:3475–9. http://www.ncbi.nlm.nih.gov/pubmed/15908656. Accessed 23 Sep 2014.
78. Pastor C, Subtil JC, Sola J, et al. Accuracy of endoscopic ultrasound to assess tumor response after neoadjuvant treatment in rectal cancer: can we trust the findings? Dis Colon Rectum. 2011;54:1141–6. http://www.ncbi.nlm.nih.gov/pubmed/21825895. Accessed 3 Nov 2014.
79. Guillem JG, Ruby JA, Leibold T, et al. Neither FDG-PET nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation

in locally advanced rectal cancer: a prospective study. Ann Surg. 2013;258:289–95. http://www.ncbi.nlm.nih.gov/pubmed/23187748. Accessed 4 Nov 2014.
80. 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. 2004;240:711–7. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1356472&tool=pmcentrez&rendertype=abstract. Accessed 22 Sep 2014.
81. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg. 2006;10:1319–28. http://www.ncbi.nlm.nih.gov/pubmed/17175450. Accessed 4 Nov 2014.
82. Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88:822–8. http://www.ncbi.nlm.nih.gov/pubmed/24495589. Accessed 2 Nov 2014.
83. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29:4633–40. http://www.ncbi.nlm.nih.gov/pubmed/22067400. Accessed 19 Sep 2014.
84. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg. 2012;256:965–72. http://www.ncbi.nlm.nih.gov/pubmed/23154394. Accessed 18 Sep 2014.
85. Vejle Hospital. Watchful waiting. An observational study of patients with rectal cancer after concomitant radiation and chemotherapy. http://clinicaltrials.gov/show/NCT00952926.
86. Maria Sklodowska-Curie Memorial Cancer Center I of O: organ preservation in elderly patients with rectal cancer. http://clinicaltrials.gov/show/NCT01863862.
87. Paulo I do C do E de S. Observation versus surgical resection in patients with rectal cancer who achieved complete clinical response after neoadjuvant chemoradiotherapy. http://clinicaltrials.gov/show/NCT02052921
88. Hospital RM. Timing and deferral of rectal surgery following a continued response to pre-operative chemoradiotherapy. http://public.ukcrn.org.uk/search/StudyDetail.aspx
89. Garcia Aguilar J and collaborators. Trial evaluating 3-year DFS in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy and TME or NOM. 2014. http://clinicaltrials.gov/show/NCT02008656.
90. Dalton RS, Velineni R, Osborne ME, Thomas R, Harries S, Gee AS, Daniels IR. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis. 2012;14(5):567–71.