

CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Should We Consider Adjuvant Therapy for Rectal Cancer After Neoadjuvant Chemoradiotherapy?



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H&O How common is rectal cancer?

AB In 2016, we can expect nearly 40,000 new cases.

H&O What is the standard treatment for locally advanced resectable rectal cancer?

AB Historically, we treated patients with stage II or III rectal cancer with surgery, followed by the “sandwich approach” of chemotherapy followed by chemoradiotherapy followed by additional chemotherapy over a 6-month period. We know from clinical trials and from years of clinical experience that the risk of local recurrence for individuals with stage II or III rectal cancer is considerable, and that surgery alone usually is not sufficient to reduce the risk.

Neoadjuvant chemoradiotherapy became the dominant treatment strategy for locally advanced rectal cancer after trials demonstrated that it is superior to surgery followed by chemotherapy, chemoradiotherapy, and more chemotherapy. Furthermore, this approach appears to be better tolerated by patients. Another benefit of neoadjuvant chemoradiotherapy is the ability to downsize tumors before surgery, which in some cases may permit a sphincter-sparing procedure.

Unfortunately, most of the trials that established the use of neoadjuvant therapy did not provide a clear body of evidence to define the role of adjuvant therapy. For example, many of the trials left the decision about whether to use adjuvant therapy to the treating physician’s discretion.

There is some variation in evaluation and treatment among the guidelines that are used around the world.

The guidelines from the National Comprehensive Cancer Network (NCCN) recommend neoadjuvant chemoradiotherapy followed by surgery and adjuvant chemotherapy for all patients with clinical stage II or III rectal cancer. These recommendations regarding adjuvant therapy in rectal cancer are extrapolated from what we know about colon cancer. The current standard of care for colon cancer is 6 months of postoperative therapy using 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX), or capecitabine and oxaliplatin (CapeOx). Oxaliplatin plus a fluoropyrimidine is the only combination that has been shown to extend survival in patients with stage III colon cancer.

Now we are beginning to question whether we should be following the same chemotherapy approach for rectal cancer as for colon cancer. Another question is whether guidelines from the NCCN and other groups should take into account the pathologic stage when considering the use of adjuvant therapy after neoadjuvant chemoradiotherapy. The European Society for Medical Oncology (ESMO) guidelines recommend adjuvant chemotherapy only for patients with stage III and high-risk stage II disease, and guidelines from the Netherlands and from Norway do not routinely recommend postoperative chemotherapy for people who were treated preoperatively with combined chemoradiotherapy. In addition, many have questioned whether adjuvant chemotherapy is necessary for patients who have a complete pathologic response to chemoradiotherapy. We have inconsistency among recommendations, which reflects our lack of definitive evidence and the need to generate more data that encompass the emerging treatment approaches for rectal cancer.

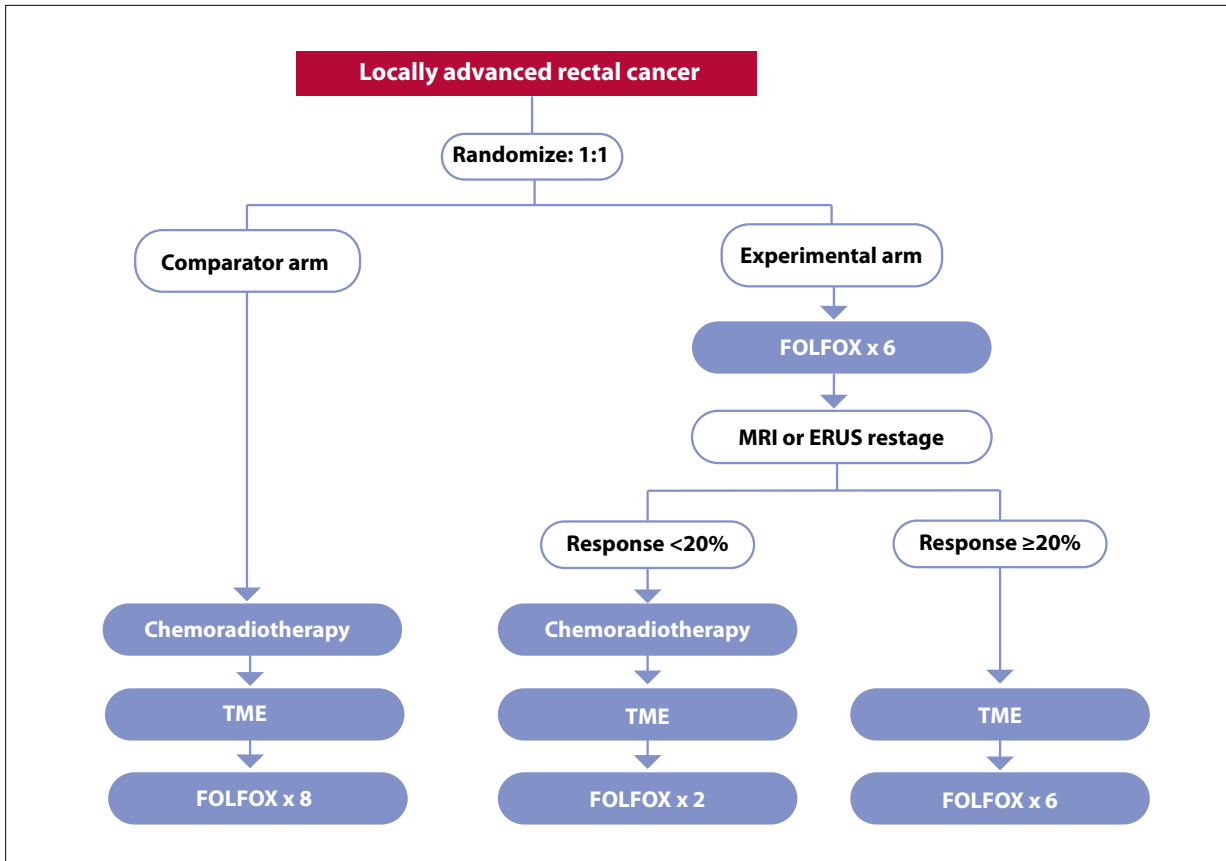


Figure. Schema for the phase 2/3 PROSPECT N1048 trial of patients with locally advanced rectal cancer (T2N1 or T3N0-1) that is 5 to 12 cm from the anal verge. Chemoradiotherapy in this trial consists of 5-FU plus radiation or capecitabine plus radiation.

ERUS, endorectal ultrasound; FOLFOX, leucovorin, 5-FU, and oxaliplatin; 5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; PROSPECT, Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery; TME, total mesorectal excision.

Source: ClinicalTrials.gov. PROSPECT: chemotherapy alone or chemotherapy plus radiation therapy in treating patients with locally advanced rectal cancer undergoing surgery. <https://www.clinicaltrials.gov/ct2/show/NCT01515787>. Identifier: NCT01515787. Accessed September 1, 2016.

H&O What other factors have made it difficult to determine the role of adjuvant treatment for patients with locally advanced resectable rectal cancer?

AB Another challenge in comparing the results of different treatment approaches is the fact that treatment of rectal cancer is multifactorial, encompassing surgery and radiotherapy as well as chemotherapy. Radiotherapy techniques have evolved over time, and the results also depend on the operational judgment of the radiation oncologist who designs the treatment. Likewise, the results of surgery depend on the type of surgery performed and the surgeon's skill. Not all patients receive a total mesorectal excision (TME), and not all procedures lead to negative margins. We do know, however, that patients who have had a TME with negative margins have improved outcomes.

Another potential factor is the location of the tumor. Patients with more proximal tumors, for example, have a reduced risk of local recurrence. Does this make them less likely to obtain additional benefit from radiotherapy? We do know that the risk of local recurrence is higher in patients with more distal rectal cancer, characterized by tumors that are no more than 5 to 6 cm from the anal verge. All of these factors are critical when it comes to integrating a multidisciplinary approach to treatment, including the use of adjuvant therapy.

H&O What role does cancer staging play in decisions about adjuvant treatment?

AB Clinical staging has improved, thanks to technical advances in magnetic resonance imaging and endoscopic ultrasound. Although we used to treat all patients with

clinical stage II or III rectal cancer in the same way, we are beginning to understand that this strategy is no longer optimal.

H&O What are some of the recent studies that have addressed adjuvant treatment in rectal cancer?

AB In a meta-analysis that was published in 2015 in the *European Journal of Surgical Oncology*, Bujko and colleagues analyzed data from 2398 patients with rectal cancer from 4 trials. All patients had received preoperative chemoradiotherapy and had been randomly assigned to postoperative chemotherapy vs observation, or to 5-FU alone vs 5-FU/oxaliplatin as postoperative chemotherapy. The investigators found a disease-free survival benefit in some trials but not in others, and little benefit to overall survival. The researchers concluded that the use of postoperative chemotherapy in patients with rectal cancer who have received preoperative chemoradiotherapy is not based on strong scientific evidence.

In a second meta-analysis that was published in 2015 in the *International Journal of Colorectal Disease*, Petrelli and colleagues analyzed data on 5457 patients from 5 randomized trials and 10 retrospective studies who had neoadjuvant treatment and surgery. The researchers found evidence that adjuvant chemotherapy improved 5-year overall survival and 5-year disease-free survival, but pointed out that the evidence of benefit derived mainly from retrospective studies.

So we have 2 analyses that have reached somewhat different conclusions. This is a good example of why controversy continues in this area, and we do not have definitive, evidence-based recommendations for adjuvant therapy.

Some experts have questioned whether we should be using older studies to determine benefit, because of variability in clinical staging and in the surgical procedure; that is, the percentage of patients who had a TME.

There are also differences in how neoadjuvant therapy is administered. European studies have looked at short-course radiotherapy, which consists of 5 days of radiotherapy—without chemotherapy—followed by surgical resection. Those studies show very good local control of cancer, and the NCCN recently added short-course radiotherapy as a strategy for neoadjuvant therapy.

When we look at the effects of adjuvant therapy, we need to take into account how the neoadjuvant therapy was administered: was it long-course or short-course? It is also critical to define populations based on American Joint Committee on Cancer (AJCC) staging. The most recent edition of the staging manual details the difference in outcome for rectal cancer based on substage: stage IIA,

IIB, IIC, IIIA, IIIB, and IIIC. Patients with stage IIIB or IIIC rectal cancer are at especially high risk for recurrence if chemoradiotherapy does not downstage their disease. Although adjuvant therapy has not been proven to benefit even these high-risk patients, clinicians may be more likely to use it for this group of individuals.

At the other end of the spectrum, it is reasonable to doubt whether a patient who had a complete pathologic response to chemoradiotherapy would benefit from the addition of adjuvant therapy, after accounting for the potential toxicity.

H&O What ongoing or future studies are being planned?

AB Because the data are inconclusive regarding the benefits of adjuvant therapy, and we know that many patients currently do not receive adjuvant therapy, a better strategy may be to focus on neoadjuvant therapy and to consider more chemotherapy as an extended neoadjuvant approach. The PROSPECT trial (Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery) from the Alliance for Clinical Trials in Oncology is enrolling patients whose tumors are at least 5 cm from the anal verge (see figure). Patients are randomly assigned to receive standard chemoradiotherapy, surgery, and adjuvant chemotherapy or FOLFOX chemotherapy (NCT01515787). Patients assigned to the neoadjuvant FOLFOX arm who have a response of 20% or better do not receive chemoradiotherapy; instead, they proceed directly to surgery followed by adjuvant FOLFOX chemotherapy. In other words, patients who have more proximal tumors may not need radiotherapy if they respond well to chemotherapy. Of course, this trial is not designed to address the role of adjuvant chemotherapy because patients in both arms of the study are receiving it.

A potential future trial would include patients with clinical stage I or II rectal cancer and distal tumors, categorized as T1 through T3 or N0, to see whether there is an increased rate of organ preservation after neoadjuvant FOLFOX followed by transanal excision of residual cancer followed by adjuvant chemoradiotherapy.

H&O What other questions would you like to see answered regarding the treatment of rectal cancer?

AB Another interesting question is whether people who have experienced a complete response to neoadjuvant treatment even need surgery, and instead can be followed by close surveillance. This is a question that is being addressed in clinical trials with carefully selected patients.

Another approach combines neoadjuvant chemotherapy and transanal excision microsurgery (TEMS) in early-stage rectal cancer. NRG Oncology—which brings together the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group—will explore new radiotherapy and systemic therapy combinations in high-risk patients (eg, radiotherapy + capecitabine/veliparib).

We may be able to glean more useful data from more modern clinical trials and databases, in which clinical staging will be better and more patients will have TME surgeries. We are increasingly recognizing that a one-size-fits-all approach is suboptimal, and that there are subsets of patients who do not require intensive combined modality treatment, including adjuvant therapy, in order to maintain organ function and long-term survival. We also must develop new strategies for those high-risk patients who do not respond optimally to current combined modality interventions.

Suggested Readings

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