Improved Patient and Regimen Selection in Locally Advanced Rectal Cancer: Who, How, and What Next?

Jared Weiss,1 Drew Moghanaki,2 John P. Plastaras,2 Daniel G. Haller1

Abstract

Before the advent of neoadjuvant chemoradiation therapy (NCRT) for locally advanced rectal cancer, local failure represented half of treatment failures. The German Rectal Cancer Study Group trial demonstrated that NCRT along with total mesorectal excision can improve local control and the rate of sphincter-preserving surgery. Thus, the National Comprehensive Cancer Network now recommends NCRT as the standard of care for stage III and IV rectal cancer. Recent trials and analysis have questioned accepted wisdom regarding patient selection for NCRT and methods of administration. EORTC 22921 demonstrated that the addition of chemotherapy to radiation therapy, regardless of timing, improved local control but not overall survival, and subgroup analysis from this study generated the hypothesis that the subgroup of patients with good pathologic response to NCRT would benefit the most from additional chemotherapy following surgery. The prognosis of rectal cancer is stage dependent, and 2 major analyses question whether T1/2 N1 and T3 N0 patients benefit from NCRT. Application of the results from these studies is hindered by imperfections in staging. Future improvement in patient selection might result from biologic analysis of tumor sensitivity. NCRT might be improved with the use of oral fluoropyrimidines and perhaps the addition of a second agent such as oxaliplatin, irinotecan, or cetuximab. Improvements in radiation, such as the use of more conformal techniques, might decrease the toxicity of therapy. Given the success of NCRT in improving local control, distant metastasis now predominates as the cause of treatment failure, and larger gains will likely be made from improvements in adjuvant chemotherapy.

Introduction

Locally advanced rectal cancer treated with surgery alone frequently results in a high risk of local relapse, especially when total mesorectal excision (TME) is not performed. For example, the New England Deaconess Hospital in Boston reviewed 168 patients treated at that institution from 1965 to 1978 and reported that 83% of patients received surgery alone and that half of recurrences were local.1 Adjuvant chemoradiation therapy, and subsequently neoadjuvant chemoradiation therapy (NCRT) have evolved to improve local control. The goals of NCRT in improving local control are improved surgical resectability and increased rates of sphincter preservation, ultimately leading to improved disease-free survival (DFS), overall survival (OS), and quality of life.

Multiple trials have demonstrated lower local recurrence and survival benefits with the addition of chemotherapy to adjuvant radiotherapy.2-4 In 1991, the National Comprehensive Cancer Network (NCCN) released a clinical announcement recommend- ing adjuvant therapy in all patients with stage II-III rectal cancer. Following this, in 2005, the German Rectal Cancer Study Group trial5 was published comparing a nearly identical chemoradiation therapy regimen administered preoperatively or postoperatively with TME. The study found improved local control with NCRT. Furthermore, among patients initially felt to require abdomino-perineal resection (APR), the rate of sphincter-preserving surgery was doubled with the use of NCRT. Thus, NCRT is now recommended by the NCCN as the standard of care for patients with stage T3/4 N0 (stage II) and node-positive (stage III) rectal cancer. These guidelines are summarized in Figure 1.

However, data has since emerged suggesting that all patients might not need or benefit from adjuvant therapy. In fact, it is possible that a large number of patients considered to have clinical stage
II or III disease might actually have stage I disease and should not be treated with NCRT. Additionally, a second important controversy has recently emerged: whether postoperative chemotherapy in patients who completed preoperative chemoradiation is necessary. Selection of adjuvant therapy is thus not straightforward. Herein, we discuss the available data regarding these controversies to help with individualized clinical decisions when considering adjuvant therapy in rectal cancer.

**Are There Patients Who Might Not Benefit From Neoadjuvant Chemoradiation?**

**Staging**

The prognosis of patients with rectal cancer is stage dependent. Two major analyses were published in 2004 to define the stage dependence of outcomes. The first retrospectively evaluated 5987 patients with stage III rectal cancer in the National Cancer Database, showing great heterogeneity among stage III patients. The second pooled data entered from 5 randomized phase III North American rectal cancer adjuvant trials (NCCTG 79-47-51, NCCTG 86-47-51, US Gastrointestinal Intergroup 0114, NSABP R01, and NSABP R02) and defined 3 risk groups. The results of these 2 analyses are shown in Table 1. Of note, treatment was heterogeneous both within each of these analyses and between them. In particular, 25% of patients in the former study did not receive any form of adjuvant therapy, compared with 5% in the latter. Two studies defined anatomically staged groups of patients who are currently considered for NCRT but who might do well with less intensive therapy. Willett et al retrospectively evaluated 117 patients with T3 N0 rectal cancer treated with surgery alone between 1968 and 1985. Of the 25 patients whose tumors exhibited favorable histologic characteristics (well-differentiated or moderately differentiated, invading < 2 mm into perirectal fat, and absence of lymphatic or venous involvement), the 10-year actuarial rates of local control and recurrence-free survival were 95% and 87%, respectively. Gunderson et al analyzed the pooled data from the 5 North American rectal cancer adjuvant trials listed above by treatment modality. One group of particular note was the “moderate-risk” group consisting of T1/2 N1 and T3 NO patients from R01 and R02, whose 5-year OS with surgery plus adjuvant chemotherapy (without radiation therapy) of 85% and 84% are comparable to published results from trimodality therapy. In summary, patients with either node-negative T3 tumors and less invasive N1 tumors might do well with either observation of adjuvant chemotherapy only, particularly for high rectal lesions, when TME is performed and when sphincter preservation is not an issue.

Imperfections in preoperative clinical staging represent an important barrier to the application of the results of Willett et al and Gunderson et al to clinical practice. Careful assessment of data reported by the German adjuvant trial raises significant concerns about overstaging. In their report, 18% of patients determined to be stage II or higher were found to harbor only stage I disease at the time of resection in the surgery up-front arm and thus might not have required potentially toxic chemoradiation. A separate study from a consortium of 6 institutions expanded concern about staging inaccuracies in the opposite direction. The study analyzed 188 patients with cT3 N0 rectal cancer as determined by endorectal ultrasound or magnetic resonance imaging (MRI). Even after patients were treated with NCRT, surgical staging revealed 22% of those initially defined cN0 patients actually had pathologically involved lymph nodes. The true incidence of pretreatment nodal involvement might thus likely be even higher as NCRT is known to downstage lymph nodes. The authors aptly titled their report “cT3N0 Rectal Cancer: Potential Overtreatment With Preoperative Chemoradiation Is Warranted.” A retrospective study from M. D. Anderson Cancer Center lends support to this concern by also showing significant numbers of unexpected positive nodes following NCRT—12% in this study.

---

**Figure 1** National Comprehensive Cancer Network Guidelines for the Treatment of Stage II and III Rectal Cancer

Abbreviations: 5-FU = 5-fluorouracil; FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin; NCRT = neoadjuvant chemoradiation therapy
Regimen Selection in Locally Advanced Rectal Cancer

Improvements in staging have been made with MRI. In the MERCURY study,\textsuperscript{11} the authors were able to use MRI to accurately ascertain depth of invasion to a mean difference of .05 mm and maximum difference of .49 mm from histologically confirmed results. However, the 18 radiologists who read the MRIs had at least 5 years of experience reporting abdominal and pelvic imaging and attended specialized imaging workshops to ensure standardization. Therefore, their results might not reflect results that will be typically obtained in the community. MERCURY also did not address nodal staging.

Improved nodal staging could potentially allow some patients with cT3 N0 to forgo NCRT. For example, the use of ultrasmall particles of iron oxide might improve MRI evaluation of nodal status in rectal cancer.\textsuperscript{12} In one study, 6 of 74 nodes examined harbored malignancy on histologic staging. Four nodes contained macrometastatic disease and were correctly identified; the other 2 contained micrometastatic disease, which might be a finding of uncertain clinical significance. The MERCURY trial has already shown that, in experienced hands, MRI can accurately stage tumor depth; if ultrasmall particles of iron oxide or other methods can extend this gain to nodal staging, then the individualization of multimodal care as proposed by Gunderson et al might be clinically applied.

Microarray Analysis

Clinical factors have been defined for prediction of pathologic complete response (pCR) in patients undergoing NCRT, such as circumferential extent of tumor < 60%, carcinoembryonic antigen < 2.5 ng/mL and distance from the anal verge of > 5 cm.\textsuperscript{10} Biologic factors might be even more important. Two groups applied gene chip analysis to predict which patients will respond to chemoradiotherapy (CRT). The first study evaluated pretherapeutic biopsies from 23 patients, with a 7-patient validation cohort on a different microarray platform. The study’s endpoint was downstaging.\textsuperscript{13} Sensitivity (correct prediction of response) was 78%, and specificity (correct prediction of lack of response) was 86%, for an overall accuracy of 83%. Similar results were obtained in a later study\textsuperscript{14} and in a study of neoadjuvant radiation therapy alone.\textsuperscript{15} The ability to predict response to NCRT based on tumor biology needs to be evaluated prospectively in larger cohorts. However, we view as promising the possibility of selecting the most efficacious curative therapy for patients based on tumor biology. With further developments of this technology, NCRT could be reserved for patients likely to respond, thereby avoiding toxicity and delay in surgery in patients who are unlikely to benefit.

What Chemotherapy Should Be Used With NCRT? 5-Fluorouracil

The current standard of combining peripheral venous infusion of 5-fluorouracil (5-FU) together with radiation was first defined in 1994 by INT 86-47-51 in the postoperative setting.\textsuperscript{16} All 661 patients in this study had stage II or III rectal cancer. Patients received an initial 9-week cycle of systemic chemotherapy and were randomized to either bolus 5-FU and semustine or bolus 5-FU alone. All patients then received radiation therapy concurrent with 5-FU chemotherapy followed by a second course of chemotherapy identical to the original course. A second randomization determined the chemotherapy administered concurrent with the radiation therapy—either bolus 5-FU or continuous infusion 5-FU. The patients who received 5-FU as a continuous infusion demonstrated increased time to relapse and improved OS; there was no benefit from semustine. There was more diarrhea in the group receiving prolonged infusion.

In contrast, such findings were not found in the more recent INT 0144.\textsuperscript{17} Here, patients were randomized to 3 different schedules of 5-FU administration. The first arm was similar to the peripheral venous infusion group from INT 86-47-51 with pre- and post-XRT bolus 5-FU. A second group was assigned to receive this same treatment but with 5-FU also by continuous infusion before, during and after radiation therapy. The third group received bolus 5-FU with leucovorin before, during, and after radiation therapy, with levamisole given before and after radiation therapy. There were no differences in OS or relapse-free survival among the groups. Only hematologic toxicity differed, with 4% grade 3 or 4 reactions in the continuous-infusion group and 55% in the bolus group. The lack of differences might have been attributable to the presence of some form of long-acting 5-FU in all 3 arms (either in the form of continuous infusion 5-FU or leucovorin-modulated 5-FU).

Can Oral Agents Be Substituted for 5-Fluorouracil Infusions?

Findings from colon cancer trials are commonly extended into use in rectal cancer. The X-ACT trial\textsuperscript{18} compared bolus 5-FU plus leucovorin to single-agent capecitabine in the adjuvant setting, DFS was at least as good in the capecitabine arm. This led to the hypothesis that capecitabine might be equivalent in other contexts, such as NCRT for rectal cancer. An M. D. Anderson Cancer Center trial\textsuperscript{19} was representative of several phase II trials that lend support to this hypothesis—pCR was 18%, with 59% downstaging and a 23% rate of grade 3 or 4 toxicity. Although we are optimistic that capecitabine is at least as efficacious as peripheral vein isolation (PVI) 5-FU, we await the results of the ongoing NSABP R04 trial before routinely applying these phase II results. This ongoing 4-arm trial compares PVI 5-FU to capecitabine, with both groups randomized to receive oxaliplatin or not during radiation therapy.

Should Other Agents Be Added to a Fluoropyrimidine?

To improve upon the results of NCRT with fluoropyrimidines, multiple retrospective and phase I and II studies have added oxali-
platin to either 5-FU or capcitabine, with pCRs of 10%-34%.20-22 A phase II trial study that added irinotecan to continuous venous infusion 5-FU demonstrated similar results, with a pCR of 28%.23 A recent meta-analysis of phase II and III trials using NCRT for rectal cancer found 3 factors that influenced pCR—the use of 2 drugs, the use of infusional 5-FU, and higher radiation therapy dose.24

Many trials are assessing the benefit of double- or triple-agent chemotherapy in NCRT. The aforementioned NSABP R04 trial is a phase III study that, in addition to assessing the equivalency of capcitabine, will likely provide the best estimate of the benefit and toxicity of adding oxaliplatin to either infusional 5-FU or capcitabine. Additional data will come from Radiation Therapy Oncology Group (RTOG) 0247, which terminated patient accrual in early 2007, comparing capcitabine with oxaliplatin to capcitabine with irinotecan in NCRT. Finally, in separate trials, both the Hospital of the University of Pennsylvania and the 3 major Harvard hospitals are assessing the value of adding cetuximab to infusional 5-FU.

**Following Preoperative Chemoradiation, Do All Patients Benefit From Postoperative Chemotherapy?**

Practice in the United States has been based primarily on the positive trials for chemotherapy versus CRT reported by O’Connell et al. This practice is further supported by the positive trials for adjuvant chemotherapy alone in nonrectal colon primaries, particularly in node-positive patients (for example).16,25,26 Furthermore, the German trial that helped establish NCRT as the standard of care used adjuvant chemotherapy beyond chemoradiation and surgical resection. After NCRT, a negative surgical evaluation might not accurately reflect the stage at presentation—the nodes could have been involved preoperatively but have been sterilized by NCRT. Current NCCN guidelines recommend further adjuvant chemotherapy following surgery for patients treated with NCRT.

Results from the EORTC 22921 trial challenged this paradigm.28 In this 4-arm phase III trial, all patients underwent preoperative radiation therapy to 45 Gy followed by surgery. Patients with clinical stage T3 or T4 resectable rectal cancers were randomized to receive either preoperative radiation therapy alone, preoperative chemoradiation therapy, preoperative radiation therapy followed by postoperative chemotherapy, or preoperative chemoradiation therapy followed by postoperative chemotherapy. Thus, half of the patients received postoperative chemotherapy and half did not. Surprisingly, the use of chemotherapy did not improve survival. However, the addition of chemotherapy in any setting, as compared with the preoperative radiation therapy–alone arm, was found to improve local control, regardless of timing. Additionally, there did not appear to be any benefit with postoperative chemotherapy, as long as patients received chemotherapy preoperatively with radiation.

There are several reasons why EORTC 22921 could have failed to discern a real clinical benefit. With only 253 patients per arm (total of 506 patients receiving postoperative adjuvant chemotherapy), the study might have been underpowered to detect a survival difference in subgroups. Furthermore, adherence to postoperative therapy was rather low compared with other published trials, with less than half of patients receiving full therapy per protocol and 28% of patients receiving no postoperative chemotherapy at all. Whether this reflects only intolerance to further therapy by patients or also a lack of commitment by participating investigators in administering full-dose therapy is speculative. Regardless, it might account for a failure to detect benefit to additional adjuvant therapy.

Post hoc analysis of EORTC 22921 generates an interesting hypothesis.29 Although the comparison between receiving and not receiving additional adjuvant chemotherapy in patients who received NCRT was not statistically significant, the authors noted a divergence in the curves of DFS at 2 years and OS at 5 years. Post hoc analysis demonstrated that the patients who were benefiting and thus causing this divergence were patients who were downstaged to yp0-2. Although these results are primarily hypothesis generating, the hypothesis is interesting: that NCRT was itself a test for chemosensitivity. Like the gene chip data, we regard this idea as particularly promising and worthy of future study because it is predictive instead of solely prognostic and could thus improve clinical decision making.

**How Best to Deliver Radiation?**

As discussed in the Introduction, when a decision is made to irradiate, it is generally considered best delivered in the preoperative setting. However, the historical development of this strategy has created an international divide in fractionation strategy. The use of conventionally fractionated radiation therapy delivered over 5 weeks with or without chemotherapy was largely pioneered in North America in the postoperative setting, whereas preoperative radiation therapy was developed in Europe with a single-week course of 5 Gy × 5 fractions delivered without chemotherapy. The Polish Colorectal Study Group trial randomized patients to this short course of radiation alone or to chemoradiation therapy with 50.4 Gy in 28 fractions of 1.8 Gy concurrent with bolus 5-FU and leucovorin.30 OS, DFS, local control, and severe late toxicity were not statistically different; only early radiation toxicity varied, at 18.2% versus 3.2%, favoring short-course therapy. Of note, adjuvant chemotherapy was not mandated in this trial.

Several concerns have limited the use of short-course radiation in North America. Controlled trials demonstrating survival advantages with adjuvant radiation therapy alone, such as the Swedish Rectal Trial,31 did not use TME, now considered the standard of care. When TME was used, neoadjuvant radiation therapy without chemotherapy was not associated with a survival benefit.32 Furthermore, in the Swedish Rectal Trial, short-course radiation was associated with a higher risk of gastrointestinal toxicity, especially small bowel obstruction.33

Phase II data for hyperfractionation demonstrated pCR rates similar to those achieved by the addition of a second chemotherapeutic drug to standard fraction radiation.34 A meta-analysis of factors affecting pathologic response suggested that dose escalation might be of benefit.24 A small phase II trial of dose escalation to 61.8 Gy with 5-FU/leucovorin in T4 and large T3 tumors showed a clinical response in half and a pCR in 25% of patients.34 Intensity-modulated radiation therapy (IMRT) has been used in other sites to escalate doses while maintaining good safety profiles.35 In anal cancer, IMRT with concurrent chemotherapy is being piloted by the RTOG in a phase II study based on decreased toxicity with similar disease control.36 In the neoadjuvant setting, initial attempts to use IMRT...
Regimen Selection in Locally Advanced Rectal Cancer

with concurrent capecitabine have had mixed safety profiles. 

Although there are limited data evaluating the role of these highly conformal radiation techniques, in principle, increased conformity perhaps combined with image-guided radiation therapy should be able to reduce toxicity and increase the therapeutic index. Proton radiation therapy might hold promise for even more conformal radiation therapy because of the lack of exit dose; however, there are no data yet evaluating proton radiation therapy in rectal cancer.

Conclusion

Major advances in the care of patients with rectal cancer can be made by individualization of care to the patient at hand. While the data are imperfect and conflicting, evidence suggests that NCRT can improve the outcomes of the patient with locally advanced rectal cancer. The ideal candidate for such therapy is the patient who, upon presentation, has a low tumor that would likely require an APR but may be converted, is clinically node positive, or has a locally advanced tumor that presents an insurmountable challenge to the surgeon to obtain a negative margin. In such patients, NCRT can offer the opportunity for potentially curative surgery and improve the rate of sphincter preservation. In contrast, the ideal patient to consider forgoing NCRT is one with a T3N0 tumor with minimal invasion into perirectal fat or a higher lesion felt amenable to low-anterior resection. The decision to forgo NCRT in such a patient would require a commitment to postoperative CRT if the patient were found to have positive or close resection margins, high-risk pathologic features, or nodal positivity.

Predictive factors are more contributory to clinical decision making than prognostic factors. Gene chip analysis, when confirmed in large prospective trials, holds the promise for selecting patients likely to respond to NCRT. We are hopeful that gene chip analysis will also ultimately help guide the choice of chemotherapy regimen and with the choice between bland XRT and chemoradiation therapy.

In recent trials, distant relapse is predominating as the etiology of treatment failure; in EORTC 22921, distant failures outnumbered local failures 3:1. This seems to be secondary to gains in local control from NCRT and improved surgical techniques.

Given the predominance of distant failure, cure rates and OS might be better improved through the use of improved adjuvant chemotherapy regimens following NCRT and surgery, and future trials should focus on this issue. NCCN defines 5-FU alone as standard of care, though there is limited data to define a regimen of choice in this setting. We believe that more aggressive regimens might improve results with adjuvant chemotherapy and possibly extend benefit to a larger group of patients.

Disclosures

Dr. Haller has served as a consultant or been on the advisory board of Genentech, Inc. and sanofi-aventis U.S.

The remaining authors have no relevant financial relationships to disclose.

References


