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Non-operative Management of Rectal Cancer: Understanding Tumor Biology

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Abstract

The management of locally advanced rectal cancer involves a combination of chemotherapy, chemoradiation, and surgical resection to provide excellent local tumor control and overall survival. However, aspects of this multimodality approach are associated with significant morbidity and long-term sequelae. In addition, there is growing evidence that patients with a clinical complete response to chemotherapy and chemoradiation treatments may be safely offered initial non-operative management in a rigorous surveillance program. Developing effective methods, such as molecular biomarkers, to predict a patient's response to therapies are therefore needed to help guide personalized treatment strategies.

The treatment of locally advanced rectal cancer focuses on a multimodality approach of systemic chemotherapy, radiation, and total mesorectal excision to maximize oncologic outcomes. While combined modality treatment for LARC results in excellent local tumor control and patient survival, the treatments are associated with significant morbidity and long-term functional complications that can impair quality of life. In addition, the tumor response to neoadjuvant therapy is quite variable. Weighed against the morbidity and significant sequelae of rectal resection, recognizing how to best optimize non-operative strategies without compromising oncologic outcomes is critical to our understanding and treatment of this disease.

Keywords

rectal cancer; chemotherapy; chemoradiation; non-operative management

Background

The management of rectal cancer has evolved significantly over the past 20 years. In particular, the treatment of locally advanced rectal cancer (LARC) focuses on a multimodality approach of systemic chemotherapy, radiation (RT), and total mesorectal excision (TME) to maximize oncologic outcomes. The German Rectal Cancer Study Group demonstrated that a technique of preoperative chemoradiation (CRT), using 50.4 gray (Gy) with concurrent IV fluorouracil (5-FU) followed by TME and adjuvant 5-FU resulted in an impressive 5-year local recurrence (LR) rate of 6%, establishing this approach as the standard of care.¹

While combined modality treatment for LARC results in excellent local tumor control and patient survival, the treatments are associated with significant morbidity and long-term

functional complications that can impair quality of life. In addition, the tumor response to neoadjuvant therapy is quite variable.² Weighed against the morbidity and significant sequelae of rectal resection, recognizing how to best optimize non-operative strategies without compromising oncologic outcomes is critical to our understanding and treatment of this disease.

Treatment response correlates with prognosis

Tumor response to neoadjuvant therapy is an important prognostic factor for LARC. Tumor regression grade (TRG) is a method to stratify primary tumor response to CRT based on histopathologic assessment of residual tumor cells and degree of tumor regression and replacement. A number of classification schemes are used, including the Mandard, Dowrak/Rödel, Memorial Sloan Kettering Cancer Center (MSKCC), and American Joint Committee on Cancer (AJCC) systems. Multiple studies have demonstrated the prognostic value of TRG systems, whereby degree of tumor response to treatment correlates strongly with improved recurrence-free survival.^{3–13}

In addition, patients with a pathologic complete response (pCR) to neoadjuvant treatment have lower rates of LR and improved survival, as compared to patients who do not achieve a pCR. In a series from MD Anderson ($n = 725$), the 5-year recurrence-free survival rates were 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively ($p < 0.001$).¹⁴ Similarly, in a pooled analysis of 14 series ($n = 3105$), the 5-year disease-free survival (DFS) for patients with pCR was 83.3% compared to 65.6% for non-pCR patients (hazard ratio, $HR = 0.44$, $p < 0.0001$).¹⁵

Factors related to tumor response

Tumor response to neoadjuvant treatment depends on a number of factors. In addition to tumor biology, the method and delivery of treatment, including the radiation dose and fractionation, the addition of concurrent chemotherapy, and the interval from completion of CRT to surgery, play an important role.

Tumor-specific factors

The majority of patients experience some degree of tumor regression after CRT, with 12–38% of cases achieving pCR. Clinical factors, such as larger tumor size and higher pretreatment clinical T and N stages, have been found to be independent predictors of poor response.^{16–20} A large, retrospective study from MD Anderson ($n = 562$) found that tumor circumferential extent $>60\%$ ($p = 0.001$), pretreatment carcinoembryonic antigen (CEA) level >2.5 ($p = 0.006$), and distance from the anal verge >5 cm ($p = 0.035$) were all associated with lower rates of downstaging.²¹ In addition, the presence of other pathologic features, such as mucinous histology, poor tumor differentiation, and ulceration, have been shown to be associated with decreased response rates.^{18–20,22}

Radiation regimens

Tumor response to neoadjuvant therapy also depends on the method and delivery of RT. Early trials using conventionally fractionated radiation doses below 35 Gy reported lower

rates of tumor response than more recent protocols using doses above 45 Gy. In one series of rectal cancer patients treated with neoadjuvant RT without chemotherapy, the rate of pCR was 17% in patients who received more than 44 Gy versus 4% in those who received less than 44 Gy ($p = 0.04$).²³ Similarly, Janjan et al. recently demonstrated that a concomitant boost of radiation to neoadjuvant CRT increased the tumor response rate, with 86% patients downstaged and 31% achieving pCR.²⁴ In a meta-analysis of 9 randomized controlled trials using various radiation doses and schedules, a direct correlation was found between radiation dose and reduction in the LR rate.²⁵ However, this finding must be interpreted in light of the known risks of RT, including radiation-induced injury, bowel obstruction, hip fractures, sexual and urinary dysfunction, proctitis, and hematologic toxicities.²⁶

Short-course versus long-course radiation

Preoperative short-course radiation therapy (SCRT; 5 Gy per day, total dose of 25 Gy) and conventionally fractionated long-course radiation therapy (1.8–2.0 Gy per day, total dose of 45–50 Gy) combined with sensitizing fluoropyrimidine-based CRT have both been shown to improve local tumor control in LARC patients.^{26,27} With SCRT, the interval to surgery may be immediate (1–2 weeks) or delayed (5–13 weeks). In a systemic review of 16 studies (retrospective studies, phase II trials, and randomized controlled trials) comparing immediate ($n = 1343$) and delayed surgery ($n = 244$) after SCRT, rates of severe post-radiation toxicity were lower (absolute difference = 4.2%), but minor postoperative complications were higher in the immediate surgery group (absolute difference = 13%). In the delayed surgery group, the pCR rates were also significantly higher (absolute difference ~10%), but there were no differences in the rates of sphincter preservation or R0 resection.²⁸

There have been two prospective randomized trials comparing SCRT with CRT. Bujko et al. analyzed 312 patients with low LARC without sphincter involvement. The proportion of patients amenable to a sphincter-sparing procedure was not different (61% SCRT versus 58% CRT, $p = 0.6$). However, in the SCRT group, the pCR rate was lower (0.7% versus 16%), and the rate of CRM positivity was higher (12.9% versus 4.4%, $p = 0.02$). There were no differences in LR, DM, overall survival, and late toxicity. The authors therefore concluded that both regimens should be considered in the treatment of LARC, though they favored SCRT based on treatment compliance, safety profile, and cost.²⁸

The more recent Trans-Tasman Radiation Oncology Group study randomized 326 patients with LARC to SCRT, early surgery, or 6 months of adjuvant chemotherapy or CRT, surgery in 4–6 weeks, and 4 months of adjuvant chemotherapy. There were no differences in the 3-year cumulative LR rates between SCRT and CRT groups (7.5% versus 4.4%, $p = 0.2$). However, it was noted that more patients in the SCRT group had distal tumors <5 cm from the anal verge (30% versus 9%). The authors therefore concluded that long-course CRT may be more effective in reducing LR for distal tumors. Similar to Bujko et al., there were no differences in late toxicity, distant recurrence, relapse-free survival, or overall survival.²⁹ In deciding whether to use SCRT versus long-course CRT, multidisciplinary considerations must be made, including the possibility of long-term toxicity and need for tumor downstaging prior to surgery.

Concurrent chemotherapy with radiation

Concurrent chemotherapy enhances the effects of radiation by improving local control.^{30,31} In multiple phase II trials of LARC patients treated with preoperative radiation alone, the pCR rates (4–13%)^{23,32–39} were notably lower as compared to those series in which patients were treated with combined CRT (9–31%).^{24,39–50} A number of randomized trials have demonstrated the benefits of adding concurrent chemotherapy to radiation, including local RT sensitization and systemic control of disease. In a study of LARC patients randomly assigned to receive preoperative CRT with 5-FU/leucovorin (LV) or RT alone, patients receiving CRT were significantly more likely to have a pCR (11.4% versus 3.6%, $p < 0.05$) and less likely to develop a local recurrence (8.1% versus 16.5%, $p < 0.05$).⁵¹ Similar results were seen in a phase III trial, with significant reductions in tumor size, pTN stage, and rates of lymphatic, vascular, and perineural invasion.⁵² However, there were no significant differences in overall survival (OS).⁵³ Similarly, a recent meta-analysis and Cochrane review comparing neoadjuvant CRT versus RT alone found higher pCR and local control rates; however, there was no significant effect on DFS or OS.^{54–57}

Regarding the type of concurrent chemotherapy, an early trial by the North Central Cancer Treatment Group compared infusional 5-FU versus bolus 5-FU, administered with postoperative pelvic irradiation. Infusional 5-FU was associated with longer 4-year OS (60% to 70%, $p = 0.005$), though the majority of patients in this study had node-positive disease.⁵⁸ More recently, a phase III trial comparing infusional 5-FU versus bolus 5-FU given concurrently with postoperative RT, found that at a median follow-up of 5.7 years, there were no differences in OS and relapse-free survival, though grade 3 and 4 hematologic toxicities were significantly higher in the bolus group (55% versus 4%).⁵⁹

Capecitabine given concurrently with RT has been confirmed to be an acceptable alternative to infusional 5-FU. In a phase III randomized trial, Hofheinz et al. randomized 401 LARC patients to receive capecitabine- or 5-FU-based CRT either pre- or post-operatively. DFS was higher in the capecitabine group than in the 5-FU group (HR 1.4, $p = 0.04$), though capecitabine was non-inferior to 5-FU with regards to 5-year OS.⁶⁰

Several large, randomized phase III trials have explored the effect of adding oxaliplatin to neoadjuvant CRT regimens. In an interim report for the STAR-01 trial comparing infusional 5-FU/oxaliplatin/RT to infusional 5-FU/RT, there was no difference in pCR (16% in both arms), though there was an increase in grade 3 and 4 adverse events in the oxaliplatin group (24% versus 8%, $p < 0.001$).⁶¹ Similarly, the NSABP R-04 trial demonstrated increased toxicity with the addition of oxaliplatin, while there were no differences in locoregional recurrence, DFS, OS, pCR, downstaging, or rates of sphincter-saving surgery.^{62,63} The ACCORD 12/0405-ProDIGE 2 trial compared concurrent capecitabine with RT to CapeOx with RT; at 3 years, there were no differences in rates of pCR, LR, DFS, or OS.⁶⁴ A randomized, multicenter phase III trial examined the effect of adding oxaliplatin to adjuvant CRT with concurrent capecitabine. Interim results showed increase in grade 3/4 toxicity, with no difference in 3-year DFS, OS, local or distant recurrences.⁶⁵

Conversely, the German CAO/ARO/AIO-04 trial compared a control group receiving CRT and concurrent infusional 5-FU, surgery, and 4 cycles of bolus 5-FU, to a study group treated with CRT concurrent infusional 5-FU and oxaliplatin, surgery, and 8 cycles of infusional 5-FU, LV, and oxaliplatin. The group receiving oxaliplatin was found to have higher rates of pCR (17% versus 13%, $p = 0.04$), as well as improved 3-year DFS (75.9% versus 71.2%, $p = 0.03$), though there were notable differences in the 5-FU schedule of each arm, which may have affected treatment responses.^{66–68} Early results from the phase III, multicenter FOWARC trial randomized patients to neoadjuvant 5-FU/LV-RT, FOLFOX-RT, or FOLFOX and reported highest rates of pCR in the FOLFOX-RT group. The authors attribute these findings to full dosing with mFOLFOX6 and a high rate of treatment compliance (>90%).⁶⁹ Based on these conflicting findings, the role of adding oxaliplatin to the concurrent CRT regimen is still unclear and it is not routinely used.

The addition of targeted agents to CRT regimens is also still being explored. In the randomized phase II EXPERT-C trial comparing neoadjuvant CapeOx, followed by capecitabine/RT, surgery, then adjuvant CapeOx, to the same regimen with the addition of weekly cetuximab, there was a significant improvement in OS in KRAS-WT patients (HR = 0.27, $p = 0.03$), though the primary endpoint of complete response rate was not met.⁷⁰ Similarly, the randomized multicenter phase II SAKK 41/07 trial evaluated the effect of adding panitumumab to neoadjuvant capecitabine-based CRT for patients with KRAS-WT LARC and found a higher combined rate of pathologic near-complete and complete tumor response as compared to capecitabine-based CRT alone (53% versus 32%, $p < 0.05$), though there were significantly higher rates of grade 3 toxicity.⁷¹ Finally, a phase II study evaluating a regimen of preoperative CapeOx/bevacizumab/RT followed by surgery then adjuvant FOLFOX/bevacizumab, demonstrated an excellent 5-year OS of 80% and relapse-free survival of 81%, though the primary endpoint of pCR was not met. There were also significant toxicities and low compliance with adjuvant therapy (only 54% started adjuvant chemotherapy and 38% completed the full course).⁷²

Interval between neoadjuvant therapy and surgery

Tumor response to CRT is time-dependent, sometimes taking months to achieve maximal tumor regression. Traditionally, the recommended interval between completion of neoadjuvant therapy to surgery is six to eight weeks, a timeframe that promotes tissue response to and recovery from radiation, but prevents development of radiation-associated tissue fibrosis. The Lyon R90-01 trial was the first to demonstrate that increasing the interval after CRT improved pathologic response rates. In this study, LARC patients ($n = 201$) were randomized to a short (2 weeks) or long (6–8 weeks) interval of rest before surgery. The long interval from CRT to surgery was associated with better clinical tumor response (72% versus 53%, $p = 0.007$) and increased rates of pCR or microscopic residual disease (26% versus 10.3%, $p = 0.005$).⁷³ At a median follow-up of 33 months, there were no differences in morbidity, LR, or survival between the two groups. The conclusion was therefore that a longer interval from radiation to surgery increases tumor downstaging, without detrimental effect on toxicity or early oncologic outcomes.

A recent meta-analysis reported an increase in pCR rates from 13.5% for an interval of 6–8 weeks to 19.5% for intervals longer than 8 weeks.⁷⁴ A retrospective review of more than 17,000 rectal cancer patients from the National Cancer Database found the optimal waiting period was 10–11 weeks, with a 27% greater odds of pCR for this interval compared to an interval to surgery of 6–8 weeks. There are multiple ongoing trials, including the Surgical Timing After Radiotherapy for Rectal Cancer Analysis of Technique (STARRCAT)⁷⁵ and Groupe de Recherche Chirurgicale sur le Cancer du Rectum-French Research Group of Rectal Cancer Surgery (GRECCAR-6),⁷⁶ to prospectively evaluate the effect of interval to surgery on long-term OS and DFS.

Findings have been similar with the use of SCRT. In the Swedish Rectal Cancer trial (n = 1316), the interval from short-course radiation to surgery averaged 10.5 days (range, 5 to 155). The proportion of surgical specimens with positive nodes in patients whose interval was shorter than 10 days was 45%, as compared to 4% in those patients with a time to surgery interval of more than 10 days ($p < 0.001$).⁷⁷ The Dutch trial of TME with or without radiation therapy confirmed that preoperative SCRT also does not significantly downstage the tumor if the radiation-to-surgery interval is less than 10 days.⁷⁸ Because the dose of radiation used in short-course preoperative protocols is considered biologically equivalent to the dose used in long-course protocols, the differences in tumor regression have been attributed primarily to differences in the radiation-to-surgery interval.

The Stockholm III trial was a randomized, multicenter, non-inferiority trial that randomized patients to receive SCRT with immediate surgery (within 1 week), SCRT with delayed surgery (after 4–8 weeks), or long-course radiation (25×2 Gy) with delayed surgery after 4–8 weeks. Early interim analysis of the SCRT groups found that of 462 patients, those randomized to SCRT with delayed surgery had earlier yp histopathologic stages and tumor categories, higher rates of pCR (11.8% versus 1.7%, $p = 0.001$), and higher rates of Dworak TRG 4 (10.1% versus 1.7%, $p < 0.001$), as compared to those patients who received SCRT with immediate surgery.⁷⁹ However, after a minimum follow-up of 2 years, there were no differences in rates of LR or distant metastasis and no differences in recurrence-free survival or OS amongst the three arms.⁸⁰ There was no difference in postoperative mortality, though postoperative and surgical morbidity were higher in the SCRT with immediate surgery group as compared to the delayed surgery groups. The authors therefore concluded that SCRT with delay is oncologically safe and noninferior to long-course RT and has the additional benefit of decreasing postoperative complications as compared to immediate surgery.

Total neoadjuvant therapy: induction chemotherapy

The technique of delivering both systemic chemotherapy and CRT in the neoadjuvant setting, prior to surgery, is known as total neoadjuvant therapy (TNT).⁸¹ The National Comprehensive Cancer Network (NCCN) guideline now considers moving treatment with systemic chemotherapy to the neoadjuvant setting prior to CRT, known as induction chemotherapy, acceptable. There are many options for induction chemotherapy, including mFOLFOX6 for eight cycles, capecitabine and oxaliplatin for five cycles,^{82–84} or weekly fluorouracil/folinic acid with biweekly oxaliplatin (FLOX)⁸⁵. Compared to the more traditional approach of CRT followed by TME then adjuvant systemic chemotherapy, the

many advantages to TNT include early treatment of micrometastases, potential for downstaging, improved delivery of planned therapy, in vivo assessment of chemosensitivity, avoiding the morbidity of having a diverting ileostomy during adjuvant chemotherapy, shortening time to ileostomy reversal, and increasing the possibility of clinical complete response (cCR).^{86–89} Numerous studies have demonstrated higher compliance and lower toxicity for TNT-based regimens, with pCR rates ranging from 11–36%.^{70,86,87,90–95}

A recent, retrospective cohort analysis at MSKCC compared 410 LARC patients treated with TNT compared to 320 patients treated with the traditional approach of preoperative CRT and planned adjuvant systemic chemotherapy.⁸⁹ Compared with the CRT and planned adjuvant chemotherapy group, patients in the TNT cohort were more likely to complete planned systemic chemotherapy (>6 cycles: 95% versus 83% for 5-FU, $p < 0.001$; 78% versus 42% for oxaliplatin, $p < 0.001$) with fewer dose reductions (26% versus 51% for 5-FU, $p < 0.001$; 54% versus 76% for oxaliplatin, $p < 0.001$), had higher rates of combined pathologic and sustained clinical response (36% versus 21%), and had shorter time to ileostomy reversal (closure within 15 weeks: 72% versus 9%, $p < 0.001$). These results highlight the advantages of TNT by allowing increased delivery of planned systemic treatment in the neoadjuvant setting. Continued follow up will be important to see the effect on long-term oncologic outcomes.

Total neoadjuvant therapy: consolidation chemotherapy

Prolonging the interval to surgery and adjuvant chemotherapy may be unsafe for patients at risk for distant metastasis. An alternative approach to TNT is CRT first followed by consolidation chemotherapy during the rest period between CRT and surgery. The Timing of Rectal Cancer Response to Chemoradiation (TIMING) trial was a multicenter prospective phase II study examining the effect of adding 0, 2, 4, or 6 cycles of consolidation FOLFOX after neoadjuvant CRT in stage II–III LARC patients. Similar to prior observations regarding the improved compliance of using induction chemotherapy in the neoadjuvant setting, in this series, 80% of patients were able to receive consolidation chemotherapy without interruption. pCR rates were significantly increased from 18% in the standard therapy group (no consolidation chemotherapy) to 38% in the group receiving 6 cycles of FOLFOX.⁹⁶

The ongoing RAPIDO trial in LARC patients is comparing standard long-course CRT followed by surgery and selective adjuvant chemotherapy to an investigational TNT group treated with SCRT followed by consolidation chemotherapy (capecitabine and oxaliplatin) and surgery. The primary outcome will be time to disease-related treatment failure (local or distant relapse or disease-specific death); the results will help determine the effect of TNT on oncologic outcomes.⁹⁷ In addition, a comparison of the effects of induction versus consolidation chemotherapy is currently being explored prospectively in the multicenter Organ Preservation for Rectal Adenocarcinoma (OPRA) trial. Patients are being randomized to CRT followed by consolidation chemotherapy or to induction chemotherapy followed by CRT.⁹⁸

For patients who achieve a cCR after TNT, there is a dilemma as to whether a potentially morbid surgical resection is still warranted. In the ongoing OPRA trial, patients in each arm

are restaged after TNT by clinical examination, endoscopy, and MRI. Patients with incomplete clinical response undergo TME, while those patients with a cCR are offered enrollment into a rigorous surveillance program to evaluate for local tumor regrowth, at which time they undergo salvage TME.⁹⁸

“Non-operative management” after neoadjuvant therapy

pCR has been well-documented after neoadjuvant treatments. In select patients with stage I disease, up to 50% achieve pCR with CRT alone. For stage II and III disease, rates of pCR are 18% with CRT alone, up to 36% with induction chemotherapy and CRT, and 38% with CRT followed by consolidation chemotherapy.^{96,99}

The concept of “non-operative management” (NOM) after cCR was first introduced by Angelita Habr-Gama in 2004.¹⁰⁰ Of 265 resectable, low rectal cancer patients who underwent CRT, 71 (27%) patients achieved a cCR at 8 weeks and were enrolled in a close observation program of monthly evaluation with digital rectal exam, proctoscopy, carcinoembryonic antigen (CEA) testing, and biopsy as needed. Those patients who developed tumor regrowth went on to surgery, while those with a sustained cCR after 1 year continued surveillance every 3 months for the next year and every 6 months thereafter. The remaining 194 patients who had an incomplete response to initial treatment underwent immediate resection, of which 22 had pCR. The cCR and pCR groups were then compared. Two patients in the cCR group developed local regrowths, one of which was salvaged with transanal excision and one with brachytherapy. There were three systemic recurrences each in the pCR and cCR groups. Over 5 years of follow-up, there was no difference in OS or DFS between the two groups. In the most recently reported outcomes, with a mean follow-up of 78 months, 5-year survival was 94% and 10-year survival was 93%. Ninety-three percent of re-growths were salvageable by TME, with a sphincter preservation rate of 86%.¹⁰¹ These results suggest that in a carefully structured surveillance program, cCR may represent cure, deferral of surgery is safe, and subsequent surgical salvage is effective.

Similarly, a group in the Netherlands reported their experience of 192 LARC patients treated with CRT; 21 patients achieved cCR and were closely followed with a non-operative management protocol. After a mean follow-up of 25 months, one patient developed local regrowth and underwent curative salvage surgery. Of patients treated with TME, 20 patients were found to have pCR. Again, overall survival and disease-free survival were no different between the cCR/NOM group and the group of patients with pCR after TME, demonstrating that with careful selection and strict surveillance, non-operative management is feasible and yields similar oncologic outcomes.¹⁰²

Araujo et al. performed a retrospective study comparing 69 patients who underwent TME and had pCR with 42 patients who achieved cCR after neoadjuvant CRT who refused surgery and therefore enrolled in a NOM protocol. A total of 12 (28%) patients in the NOM group developed disease relapse at a median of 2 years of follow-up; 5 patients developed a local regrowth, 3 developed distant metastasis, and 4 developed both local and distant disease. Four of the patients with isolated LR had successful salvage surgery. While DFS was lower in the NOM group (61% versus 83%, $p = 0.01$), there was no difference in OS.¹⁰³

More recently, in the Netherlands, the Organ Preservation Program reported their experience for patients who achieved both cCR and near cCR after neoadjuvant CRT. For patients achieving cCR, non-operative management was offered. For near cCR, an option of transanal endoscopic microsurgery (TEM) or close surveillance was offered. Overall, comparing the TEM and NOM groups, there were no differences in 3-year local regrowth-free survival (80% versus 85.8%, $p = 0.57$), distant metastasis-free survival (93% versus 97.4%, $p > 0.5$), and OS (100% versus 96%, $p > 0.5$). The authors concluded that such an approach for selected patients with cCR or near cCR was an oncologically safe strategy.¹⁰⁴

Appelt et al. performed a prospective observational study of 51 low rectal cancer patients treated with high-dose CRT (60 Gy tumor + 5 Gy endorectal brachytherapy boost). They reported an impressive cCR in 40 (78%) patients, who were then allocated to close surveillance. Over a median follow-up of 24 months, there were 9 local regrowths, of which, all were salvaged with R0 resections.¹⁰⁵

A group from the United Kingdom (OnCoRe project) reported a multi-institutional study comparing 129 patients with cCR after CRT and treated with NOM versus 228 patients who underwent surgical resection after CRT, independent of pathologic stage.¹⁰⁶ After a median follow-up of 33 months, 44 (34%) patients in the NOM group had local regrowth, of which 36/41 (88%) patients with non-metastatic local regrowths were successfully salvaged. The group then performed a propensity-score matched cohort analysis, with one-to-one paired cohorts (109 patients in each group). There were no differences in 3-year non-regrowth DFS between the NOM and surgical resection groups (88% versus 78%, $p = 0.22$), while the colostomy-free survival rates were 74% versus 47%, respectively. The group therefore concluded that NOM can be safely performed in a multi-institutional setting. However, these results must be interpreted with caution; as previously discussed, positive tumor response to treatment is associated with improved outcomes. Therefore, there is likely significant selection bias in the OnCoRe study since patients with cCR are compared to patients without cCR without accounting for pathologic stage.

At MSKCC, 32 patients who achieved cCR after neoadjuvant treatment between 2006 and 2010 were compared to 57 patients who had a pCR after TME during the same time period. The pCR group had more proximal tumors, received more adjuvant therapy, and had more advanced tumors compared to the cCR group. During a median follow-up of 23 months, 6 (21%) of the NOM patients developed local regrowth, 3 of whom also had concurrent distant recurrence. All 6 local failures were controlled with salvage rectal resection. There were no local failures in the pCR group. Overall, there were no differences in 3-year DFS or OS between the two groups.¹⁰⁷ In a subsequent update to this series, 113 patients with cCR treated with NOM were compared to 136 patients treated with TME who had pCR between 2006 and 2015. Local regrowth occurred in 22 (19.5%) patients in the NOM group, of which all 22 received salvage surgery, with 20 patients (91%) free of pelvic progression at last follow-up. A total of 93 (82%) of patients treated with NOM achieved rectal preservation. At a median follow-up of 43 months, 5-year overall survival was lower in NOM versus pCR groups (73% [95% CI 60–89] NOM versus 94% [95% CI 90–99] pCR). Within the NOM group, patients with local regrowth also had higher rates of distant metastasis, as compared to those patients without local regrowth (36% versus 1%, $p < 0.001$). These findings

highlight the need to endorse these practices with caution and to improve methods for risk stratification and patient selection for NOM.^{108,109}

In a systematic review and meta-analysis of 23 studies that used a NOM approach after cCR following neoadjuvant CRT, a total of 867 patients were examined over a median follow-up of 12–68 months. The 2-year local regrowth rate was 15.7%, with 95.4% of patients undergoing successful salvage. There were no differences in recurrence, cancer-specific mortality, and OS between NOM patients and those with pCR after TME. However, DFS was better in the surgery group.¹¹⁰

In sum, these series suggest that NOM may be an alternative approach to TME in highly selected patients with LARC who achieve a cCR to neoadjuvant therapy (Table 1). However, the data on NOM must be interpreted with caution — many of the studies are based on retrospective institutional case series of heterogeneous groups of patients, with relatively short follow-up. In addition, patient selection criteria and treatment regimens are variable, surveillance protocols are inconsistent, and definitions of response are non-uniform.

Assessing clinical response to treatment

Clinical outcomes are significantly influenced by definition of response to treatment, and often times it is difficult to distinguish between post-treatment scar and residual tumor. While there is currently no uniform or validated method for assessing response, there is a general consensus that a combination of digital rectal exam, endoscopy, and imaging studies should be used. In general, a normal digital rectal exam and a flat white scar (with or without telangiectasia) are good predictors of pCR, whereas superficial ulcerations or palpable nodularity indicate an incomplete response.¹¹¹ A combination of physical exam, endorectal ultrasound, diffusion-weighted MRI sequences, CT, and PET scan all provide an estimate of tumor regression but none are sensitive enough to perfectly predict pCR.^{112,113} Caution must also be used in interpreting negative biopsies of residual mucosal abnormalities after neoadjuvant therapy. In one study of ypT2–4 rectal cancer patients who received neoadjuvant CRT followed by surgery, only 13% of patients had residual tumor in the mucosa, whereas 98% had cells in the muscularis propria.¹¹⁴ Similarly, Smith et al. found that residual tumor cells could spread as far as 9 mm beyond the lateral border of residual mucosal abnormalities.¹¹⁵ While there are currently no validated criteria defining clinical and radiologic response to treatment, a three-tier system is currently being studied in the prospective OPRA trial (Table 2).⁹⁸

Molecular biomarkers to predict response

One of the major challenges in rectal cancer care is determining in advance which patients would benefit from neoadjuvant therapies. Such predictive markers would allow clinicians to optimize oncologic and functional outcomes for those patients likely to respond to treatment, while avoiding significant toxicity and morbidity for those patients unlikely to respond. Accurate genetic or molecular profiles that can predict treatment response in rectal cancer would have enormous implications for designing personalized treatment plans, including

rectal preservation. In addition, patients predicted not to respond could be guided to alternative therapies or proceed directly to primary surgical resection.¹¹⁶

To date, the accuracy of predicting pCR from cCR, using clinical, imaging, and histologic assessments, is not perfect.^{111,117–119} Similarly, genetic or molecular profiles that can guide clinical decision making are limited. While numerous groups have reported multigene signatures correlating with treatment response or lack of response, there has been little to no overlap of included genes, making external validation difficult.^{120–125} In one study, a cohort of gene expression profiles from pretreatment biopsies of 51 rectal cancer patients was used to validate previously published predictive signatures; the sensitivity ranged from 21–50% and specificity 30–70%.¹²⁶ The difficulties in identifying accurate predictors are many and complex, due primarily to the vast heterogeneity of patients and methodologies, including treatment regimens (e.g., type, duration, intervals), assessment of treatment response, tissue processing and other technical issues, varied platforms, and tumor heterogeneity.¹²⁷

However, from these predictive gene signature studies, a number of molecular targets have been identified for future study to better understand and improve treatment response. Proteins involved in a number of pathways, including DNA repair (XRCC2,¹²⁸ ATM,¹²⁹ MRE11,¹²⁹ Paf15,¹³⁰ PLK1,¹³¹ and VRK-1/-2¹³²), cell proliferation (c-MYC and PCNA,¹³³ GOLPH3,¹³⁴ FAK,¹³⁵ FGFR4,¹³⁶ and NF- κ B^{137,138}), cell adhesion (PLEC1¹³⁹ and DSG3¹⁴⁰), cell motility (TAGLN¹³⁹), autophagy (Beclin1¹⁴¹), apoptosis (survivin,¹⁴² APAF-1 and COX2¹⁴³), and metabolism (VNN1,¹⁴⁴ HSD17B2 and HMGCS2,¹⁴⁵ TKT,¹³⁹ and HADHA¹³⁹), have all been implicated as potential biomarkers that are dysregulated by CRT. Some studies have demonstrated that increased expression of epidermal growth factor receptor (EGFR) predicts decreased pathologic response to preoperative RT and CRT,^{146–148} and a specific polymorphism in the EGFR promoter region has been associated with treatment response.¹⁴⁹ Overexpression of cyclooxygenase-2 has also been associated with a poor response to CRT.¹⁵⁰ Similarly, cancer-initiating cells,^{151–153} cytokines that influence response,¹⁵⁴ and specific pathways involved in angiogenesis, apoptosis, cell cycle regulation, hypoxic response, and 5-FU all appear to play roles in treatment response.^{116,125} Mutations in KRAS^{155,156} and p53 have also been found to correlate with poor pathologic response. In a meta-analysis of 1830 patients from 30 studies, an association was found between wild-type p53 and improved response to neoadjuvant CRT (pCR risk ratio = 1.65, p = 0.003).¹⁵⁷

The composition of the tumor immune microenvironment may also offer insight into the predicted response to neoadjuvant treatment. McCoy et al. evaluated tumor-infiltrating lymphocytes (TILs) in 128 patients treated with neoadjuvant CRT and found that low stromal Foxp3+ cell density was significantly associated with pCR (adjusted odds ratio = 5.27, p = 0.006).¹⁵⁸ Similarly, high CD8+ TILs, high CD4+ TILs, or low myeloid-derived suppressor cells was correlated with good response to neoadjuvant CRT (p = 0.022, 0.022, and 0.005, respectively).¹⁵⁹ The role of PD-L1 (programmed death-ligand 1), an immune checkpoint protein that acts as a co-inhibitory factor, is less clear; one study demonstrated that low PD-L1 expression both before and after CRT is a negative prognostic marker¹⁶⁰, while another study demonstrated high PD-L1 expression after CRT was associated with vascular invasion, tumor recurrence, and poor recurrence-free and overall survival.¹⁶¹

Differential microRNA (miRNA) expression has also been associated with response to neoadjuvant treatment. Gaedcke et al. prospectively collected samples from 57 patients with LARC prior to treatment with CRT and surgery and compared the miRNA expression profiles in tumor and matched normal mucosa samples. Twenty differentially expressed miRNAs were significantly upregulated and 29 were downregulated ($p < 0.001$) in the tumor samples versus normal; these findings were validated by quantitative real-time RT-PCR in an independent dataset. Overexpression of miR-135b was associated with a more favorable prognosis, significantly correlating with TRG (correlation = 0.2, $p = 0.01$), as well as improved disease-free survival ($p = 0.042$) and cancer-specific survival ($p = 0.0005$).¹⁶² Carames et al. found that pretreatment miR-21 expression could distinguish complete from incomplete response, with an area under the curve (AUC) of 0.78, sensitivity 86.6%, specificity 60%, and an odds ratio of incomplete response 9.75 ($p = 0.01$).¹⁶³

Effective serum biomarkers offer obvious advantages in the treatment and early prognostication of rectal cancer treatment. Serum CEA is a known marker for prognosis and disease monitoring in colorectal cancer, and the association between elevated CEA levels and decreased response to neoadjuvant CRT has been reported.¹⁶⁴ In a recent study by Probst et al., serum from 18,113 LARC patients from the National Cancer Data Base was analyzed, and elevated CEA levels prior to neoadjuvant CRT was independently associated with decreased pCR (OR = 0.65, $p < 0.001$), tumor regression (OR = 0.74, $p < 0.001$), tumor downstaging (OR = 0.77, $p < 0.001$), and overall survival (HR = 1.45, $p < 0.001$).¹⁶⁵ Exact cutoffs for CEA levels to guide clinical decision making have yet to be validated with sufficient sensitivity and specificity.¹⁶⁴

Other serum biomarkers that are associated with improved treatment response have been studied with varying degrees of accuracy, including elevated pretreatment levels of fibrinogen¹⁶⁶ and carbonic anhydrase 9 (CAIX)¹⁶⁷ and differential expression of circulating peptides¹⁶⁸ and metabolites.¹⁶⁹ Decreased expression of certain miRNAs in serum has also been correlated with increased treatment response rates, including miR-125b (AUC = 0.782, $p = 0.009$)¹⁷⁰ and miR-345 (AUC = 0.69–0.75, $p < 0.01$); miR-345 expression is also correlated with increased 3-year local recurrence-free survival (HR = 0.14, $P = 0.002$).¹⁷¹ Circulating tumor cells (CTC) may also offer insight into tumor response; Magni et al. found that CTCs in peripheral blood decreased after neoadjuvant CRT in responders, while there was no significant change in nonresponders.¹⁷² Similarly, Sun et al. reported that after neoadjuvant CRT, CTC counts were significantly lower in 64 responders, as compared to 51 nonresponders (3.61 versus 12.08, $p < 0.001$), while at baseline, CTC counts of responders were significantly higher than those of nonresponders (44.5 versus 37.67, $p = 0.012$).¹⁷³ The same group found that MGMT promoter methylation in plasma cell-free DNA was significantly higher at baseline in responders compared to nonresponders ($p = 0.04$).¹⁷⁴

The expression of factors involved in host immune response have also been shown to vary in response to neoadjuvant treatment. Tada et al. reported that levels of IL-6 and TNF- α after neoadjuvant CRT were significantly higher in nonresponders compared to responders; conversely levels of CD40-ligand and CCL-5 were significantly lower in responders compared to nonresponders.¹⁷⁵

Caputo et al. examined neutrophil-to-lymphocyte ratio (NLR) in 87 rectal cancer patients before and after neoadjuvant CRT. They found that higher NLR and derived NLR after neoadjuvant treatment was associated with poor response to CRT and postoperative complications.¹⁷⁶ A recent meta-analysis of seven cohorts found that elevated NLR was also associated with poor OS (HR = 13.4), DFS (HR = 4.37), and relapse-free survival (HR = 3.64).¹⁷⁷

Several specific genomic alterations associated with treatment response have been identified. In one genome-wide screen, 9 single-nucleotide polymorphisms (SNPs) were found to be associated with improved response to neoadjuvant CRT. In particular, coronin 2A (CORO2A) rs1985859 was associated with positive histopathologic response to CRT ($p = 0.01$), a finding that was validated in 113 rectal cancer patients.¹⁷⁸ Patients that are homozygous C/C genotype in MTHFR gene (rs1801133) were also found to be more likely to respond to CRT (HR = 2.91, $p = 0.015$) and more likely to not experience recurrent disease (HR = 3.25, $p = 0.008$).¹⁷⁹ Similarly, SNPs in the genes associated with miRNA processing (rs745103, rs744910, and rs1722821 for SMAD3; rs6088619 for TRBP; and rs10719 for DROSHA) have also been reported to be significantly associated with CRT response in 265 LARC patients.¹⁸⁰

There has been a wealth of investigation into understanding rectal cancer response to neoadjuvant treatments. While a number of molecular biomarkers have been proposed as predictors of response, these findings must all still be validated in large independent cohorts. Standardized tissue processing techniques and experimental methodology in prospectively designed studies are needed, in order to successfully validate these potential biomarkers across various patient demographics.¹²⁷

Summary

Advances in clinical research have resulted in a treatment paradigm of chemotherapy, chemoradiation, and surgical resection for locally advanced rectal cancer, a strategy which provides excellent local tumor control and overall survival. In addition, there is growing evidence that patients with a clinical complete response to chemotherapy and chemoradiation treatments may be offered initial non-operative management in a rigorous surveillance program, without compromising oncologic outcomes. Aspects of multimodality treatment are associated with significant morbidity and long-term sequelae that can permanently impair a patient's quality of life. Therefore, effective methods to predict a patient's response to therapies are urgently needed. The next phase in the advancement of rectal cancer treatment lies in the identification and rigorous validation of molecular biomarkers to help guide personalized management strategies in the clinical setting.

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Outcomes of LARC after CRT treated with non-operative or operative management in high-volume centers. (Adapted with permission.^{26,181})

Table 1

Reference	eCR (NOM)	pCR (OM)	Isolated LR in NOM		Salvage (%)	Survival		Permanent stoma (NOM versus OM)
			Number (%)	Median interval (mos)		OS, NOM versus OM (p-value)	DFS, NOM versus OM (p-value)	
Habr-Gama et al., 2004 ¹⁰⁰	71	22	2 (3%)	60	2 (100%)	5yr: 100% versus 88% (<i>p</i> = 0.01)	5yr: 92% versus 83% (<i>p</i> = 0.09)	0% versus 41%
Maas et al., 2011 ¹⁰²	21	20	1 (5%)	22	1 (100%)	2yr: 100% versus 93% (<i>p</i> = 0.23)	2yr: 89% versus 91% (<i>p</i> = 0.77)	0% versus 45%
Araujo et al., 2015 ¹⁰³	42	69	5 (12%)	24	4 (80%)	5yr: 72% versus 90% (<i>p</i> = 0.32)	5yr: 61% versus 83% (<i>p</i> = 0.04)	7% versus 19%
Smith et al., 2018 ¹⁰⁹	113	136	22 (19.5%)	11	20 (91%)	5yr: 73% versus 94% (<i>p</i> < 0.05)	5yr: 75% versus 92% (<i>p</i> > 0.05)	10% versus 15%

LARC, locally advanced rectal cancer. CRT, chemoradiation. NOM, non-operative management. OM, operative management. cCR, clinical complete response. pCR, pathologic complete response. OS, overall survival. DFS, disease-free survival. NS, not significant.

Table 2Memorial Sloan Kettering regression schema after neoadjuvant therapy. (Adapted with permission.⁹⁸)

	Complete Response	Near Complete Response	Incomplete Response
Endoscopy	<ul style="list-style-type: none"> Flat, white scar Telangiectasia No ulcer No nodularity 	<ul style="list-style-type: none"> Irregular mucosa Small mucosal nodules or minor mucosal abnormality Superficial ulceration Mild persisting erythema of the scar 	<ul style="list-style-type: none"> Visible tumor
Digital Rectal Exam	<ul style="list-style-type: none"> Normal 	<ul style="list-style-type: none"> Smooth induration or minor mucosal abnormalities 	<ul style="list-style-type: none"> Palpable tumor nodules
MRI-T2W	<ul style="list-style-type: none"> Only dark T2 signal, no intermediate T2 signal AND <ul style="list-style-type: none"> No visible lymph nodes 	<ul style="list-style-type: none"> Mostly dark T2 signal, some remaining intermediate signal AND/OR <ul style="list-style-type: none"> Partial regression of lymph nodes 	<ul style="list-style-type: none"> More intermediate than dark T2 signal, no T2 scar AND/OR <ul style="list-style-type: none"> No regression of lymph nodes
MRI-DW	<ul style="list-style-type: none"> No visible tumor on B800–B1000 signal AND/OR <ul style="list-style-type: none"> Lack of or low signal on ADC map Uniform, linear signal in wall above tumor is ok 	<ul style="list-style-type: none"> Significant regression of signal on B800–B1000 AND/OR <ul style="list-style-type: none"> Minimal or low residual signal on ADC map 	<ul style="list-style-type: none"> Insignificant regression of signal on B800–B1000 AND/OR <ul style="list-style-type: none"> Obvious low signal on ADC map