Multi-modality Therapy for Rectal Cancer—
Past, Present, and Future

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Abstract
The treatment of rectal cancer currently involves coordinated efforts for combined modality therapy with pre-operative chemoradiation followed by surgical management and additional adjuvant chemotherapy. The landscape of rectal cancer has shifted significantly over the past 30 years. This review aims to track this changing landscape, with a particular focus on current research and future endeavors.

Over the past three decades, the treatment of rectal adenocarcinoma has evolved from a predominantly surgical disease to one involving combined triple-modality therapy with chemotherapy, radiation therapy, and surgery. Optimizing combined modality therapy for rectal cancer has been the subject of many trials involving radiotherapy techniques, chemotherapy regimens, and surgical approaches—and the optimal timing of all modalities. Current research continues to investigate optimization of these modalities for improved reduction in recurrent disease, decrease in morbidity, and increase in overall survival.

Past Treatment
Prior to the 1980s, patients with rectal cancer were predominantly treated with resection. The surgical technique was not standardized, resulting in inconsistent circumferential and distal margins, and technical difficulty of a low pelvic anastomosis frequently led to the need for a permanent colostomy in many instances. Prior to the understanding of the importance of total mesorectal excision (TME), surgical resection led to significant local failure rates, generally about 30–40 %, and up to 67 % in some series with advanced staged disease.[1–3] To reduce local failure rates, radiation was added postoperatively with a subsequent decrease in recurrence rates to around 20 %.[4–11] Meta-analyses published in 2000 and 2001 further supported the benefit of the addition of radiotherapy over surgery alone.[12,13] The Colorectal Cancer Collaborative Group published a meta-analysis in 2001 that evaluated 22 randomized trials comparing radiotherapy either before or after surgery to surgery alone. There was a trend toward an improvement in survival in the patients that received radiotherapy compared with surgery alone and support for the use of radiotherapy to reduce isolated local recurrences from 22 to 12.5 %.[12] With increasing agreement regarding the benefit of radiotherapy, it achieved widespread use by early 2000. The role of chemotherapy, while clear for

colon cancer, was not as clear for rectal cancer. However, three large studies supported the addition of 5-FU-based chemotherapy to radiation and surgery for the treatment of rectal cancer.[14–16] The GITSG-7175 trial examined patients with Dukes Stage B2, C1 or C2 (corresponding to stage II or III) disease randomized to surgery alone, postoperative radiotherapy, postoperative chemotherapy with 5-FU/methyl-CCNU, or combined chemoradiotherapy (CRT) with radiation and 5-FU/methyl-CCNU. Overall, this study showed that recurrence rates were highest in the group that received surgery alone and lowest in the group that received adjuvant radiation plus chemotherapy.[14] The NSABP R-01 trial further supported the use of systemic therapy. Patients with resected stage II or III disease were randomized to observation, adjuvant chemotherapy with methyl-CCNU/vincristine/5-FU (MOF) or postoperative radiation therapy. Although there was no combined modality treatment arm, there was an improvement in disease-free survival in patients receiving postoperative chemotherapy compared with surgery alone or postoperative RT alone.[15] The Mayo Clinic/North Central Cancer Treatment Group (NCCTG) further confirmed the role of CRT. Patients with stage II or III rectal cancer were assigned to postoperative RT alone or postoperative RT plus bolus 5-FU (in addition to a cycle of bolus 5-FU/methyl-CCNU before and after CRT). Postoperative CRT resulted in a 47 % reduction in the risk of relapse and a 36 % reduction in the risk of cancer-related death.[16] Although use of methyl-CCNU is no longer used, the National Institutes of Health consensus conference endorsed the use of postoperative 5-FU based CRT for patients with stage II or III rectal cancer.[17]

Present Treatment
Although the addition of postoperative CRT improved outcomes, the rate of local pelvic recurrences remained high, leading to significant morbidity. Improvements in surgical methods, with TME, were an important advance

to reduce the rate of local relapses.[18–20] TME now defines a specific surgical technique that includes sharp dissection to preserve the mesorectal fascia, nerve preservation whenever possible, and attention to avascular tissue planes and maintenance of hemostasis. While some upper rectal tumors may be amenable to a 'tumor-specific' mesorectal excision, mid and distal rectal cancers require a TME. Because of the dramatic reduction in local recurrence rates with TME, it is important to note whether TME was performed when comparing clinical trials. With increasing consensus regarding the benefits of CRT, attention shifted to the timing of therapy: before or after resection. The use of pre-operative CRT is supported by several randomized trials conducted worldwide.[21–24]

The National Surgical Adjuvant Breast and Bowel Project R-03 (NASBP-R-03) was developed to investigate best timing for the administration of multimodality therapy.[21] In this study, 267 patients were randomly assigned to either received pre-operative CRT (n=130) or postoperative CRT (n=137). Pre-operative treatment utilized weekly bolus 5-FU/leucovorin (LV) for 6 weeks followed by concurrent CRT using 5-FU/LV for 5 days during the first and fifth week of radiation (45 Gy with a 5.4 Gy boost), followed by weekly 5-FU/LV for 6 weeks. The postoperative treatment schedule was identical. Importantly, the pre-operative treatment arm had a statistically improved disease-free survival with a hazard ratio of 0.629 (p=0.011) and a trend in improved overall survival. Consistent with a treatment effect, patients assigned to the pre-operative arm had a lower incidence of node positive disease (p=0.04). Moreover, in the evaluable patients who received pre-operative therapy, 15 % had a pathologic complete response (pCR); and patients who were noted to have a complete response had a lower cumulative incidence of recurrence (0 versus 24.7 %; p=0.04). However, the low accrual (267 of the planned 900 patients) limited the ability to demonstrate a statistically significant improvement in overall survival. Moreover the lack of standardized surgical techniques further confounded this study and also likely contributed to failure to demonstrate an improvement in local recurrence or sphincter salvage rates in the pre-operative group.[21] Nevertheless, the biologic treatment affect seen by CRT and the improvement in disease-free survival continued to drive research into optimizing pre-operative therapy.

The German Rectal Cancer Study Group (CAO/ARO/AIO-94) provided important data demonstrating the benefits of pre-operative CRT.[22] In this large study, over 800 patients with T3 or T4 rectal cancer were randomized to pre-operative treatment with RT/5-FU followed by surgery versus surgery followed by RT/5-FU. Both treatment arms included an additional four months of 5-FU alone. In contrast to the NSABP R-03,[21] TME was the required surgical management in the German trial. Importantly, there was a statistically significant improvement in local relapse rates in the pre-operative treatment arm (6 versus 13 %), which persisted at 10 years.[25] Moreover, in the pre-operative arm, sphincter preservation was demonstrated for low rectal tumors and fewer treatment-related toxicities were observed. Although long-term follow-up did not demonstrate an improvement in overall survival, these findings led the adoption of pre-operative CRT as a mainstay in the multi-modality management of rectal cancer.[22] A Korean Trial additionally suggested a benefit for a pre-operative CRT approach.[23] This single institution study randomized 240 patients to either pre-operative or postoperative capecitabine with RT followed by four cycles of capecitabine or 5-FU. Although publication of the German Study[22] led to the low accrual/early closure in the Korean trial,

patients with low-lying tumors treated with pre-operative CRT similarly demonstrated a higher rate of sphincter-sparing surgeries.[23]

The delivery of 5-FU varied considerably between the various trials described above. Currently, however, continuous infusion 5-FU has been adapted by most institutions based on the NCCTG[26] and INT-0114[27] trials suggesting that infusional 5-FU has improved efficacy and decreased hematologic toxicities compared to bolus 5-FU regimens. Substitution of oral capecitabine with RT in lieu of infusional 5-FU is also an option.[28,29] However, because of potential issues of patient compliance, variability in bioavailability/correct dosing, and toxicities, such as hand–foot syndrome, our institutional preference is to utilize infusional 5FU whenever possible.

The dose of pelvic radiotherapy has traditionally ranged between 45–54 Gy in most of the prospective studies, many of which were performed prior to the widespread availability of modern 3D conformal treatment planning. There may also be a role for increasing the overall dose of radiotherapy in order to increase the likelihood of obtaining a pCR.[30] Modern radiation techniques continue to improve on minimizing the toxicities of conventional fractionated radiation therapy with 5FU-based chemotherapy, including the use of short-course pre-operative radiation. The advantages of short-course RT alone include a shorter time to surgery, lower relative cost, and potentially shorter overall treatment course for all therapy. Additionally, short-course pre-operative radiation can be employed in selected circumstances, such as active inflammatory bowel disease or other comorbid medical conditions[31] that preclude standard fractionation. Disadvantages of short-course radiation include the inability to observe an in vivo response to novel systemic treatments, no opportunity for tumor downstaging, as well as the lack of early systemic therapy to address potentially micro-metastatic disease. Short-course radiation in the Swedish and Dutch trials demonstrated improved local recurrence rates and disease-free survival; with the Swedish trial additionally documenting improvements in overall survival.[11,32] Smaller trials using short-course radiation also suggest equivalence to conventional radiation (Polish and Trans-Tasman Radiation Oncology Group [TROG] trials).[33,34] However, at the present time, most US centers prefer conventional fractionation.

Future

While pre-operative CRT is the current recommended care for most patients with T3 or T4 rectal cancers, research continues to evaluate methods to optimize therapy. Improvement in overall survival remains the gold standard to judge a new therapy superior to the current standard. However such trials often require large numbers and lengthy follow-up. Therefore, utilizing surrogate endpoints for the pre-operative treatment of rectal cancer might be useful in clinical trials. In rectal cancer, utilizing pCR rates is one potential proxy. In previous large trials[21,22] subgroup analysis of patients who achieved a pCR has not shown a difference in clinical outcomes such as overall survival. However, it is important to note in these larger trials only a small number of patients had a complete response. Moreover, a meta-analysis by Maas et al. evaluated 3105 patients across 17 separate datasets and found that pCR was associated with improvements in local recurrence, distant metastasis, disease-free survival, and overall survival.[35] Thus, pCR may an appropriate surrogate marker for outcomes in rectal cancer and many research trials have been designed with pCR as a primary endpoint.

Optimizing Combined Modality Therapy

Both the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSIAC) and the NSABP C-07 trials showed that the addition of oxaliplatin to 5-FU/LV improved outcomes in the adjuvant setting.[36–38] Moreover, response rates with FOLFOX chemotherapy are higher than 5-FU alone in the metastatic setting.[39,40] Therefore it was logical to attempt to incorporate oxaliplatin into pre-operative CRT rectal cancer protocols. Unfortunately this concept has been disappointing as four separate studies (NSABP R-04, ACCORD 12, STAR and CAO/ARO-04 trials) failed to demonstrate a benefit (with added toxicity) to adding oxaliplatin to pre-operative CRT compared with 5-FU alone based pre-operative CRT.[29,41–43] The addition of biologics (such as bevacizumab or cetuximab) to pre-operative CRT has not demonstrated significant added efficacy, although definitive large phase III studies are lacking.[44–48] An ongoing trial in the UK (ARISTOTLE) is examining the utility of the incorporation of irinotecan into pre-operative CRT (www.controlled-trials.com/ISRCTN09351447). Nonrandomized trials have suggested a potential benefit for the addition of irinotecan to pre-operative CRT;[49–51] however, a randomized phase II RTOG trial showed no improvement.[52] Given that irinotecan is not active in the adjuvant setting,[53–55] it will be difficult to envision the practice-changing addition of irinotecan to pre-operative CRT regimens based on the results of a single trial. Thus, the chemotherapy backbone for pre-operative CRT remains continuous infusion 5-FU alone or capecitabine.

Need for Radiation Therapy?

Despite the failures of improving on combination chemotherapy plus radiation, an alternative approach to improve pre-operative therapy is to administer modern chemotherapy alone pre-operatively. Several small studies have demonstrated high pCR rates (up to 27 %) using pre-operative FOLFOX without the added toxicities of radiation therapy.[56,57] Based on these results, the large randomized phase III PROSPECT trial will test if it is possible to eliminate radiation therapy in patients who have a good response to induction FOLFOX chemotherapy. In this trial, patients will be randomized to a standard therapy arm (pre-operative 5-FU/RT, followed by TME, and then eight cycles of postoperative FOLFOX). In the experimental arm, all patients will undergo six cycles of pre-operative FOLFOX. Patients demonstrating progression or responses <20 % will receive pre-operative 5-FU/RT, followed by TME, and then two more cycles of postoperative FOLFOX. However, patients demonstrating good responses (>20 %) will proceed to TME (without pre-operative RT), and then six cycles of postoperative FOLFOX. The final primary endpoints will be R0 resection rates, time-to-local recurrence, and disease-free survival rates. It will be interesting to see if these selected patients who forego RT will have equivalent outcomes compared to standard therapy—but without the added toxicity of RT.

Optimal Timing of Surgery?

Another approach to improve pCR rates has focused on optimizing the timing between pre-operative CRT and surgery. Historically, studies that have looked at longer intervals between pre-operative CRT and surgery demonstrate improved pCR rates, but pelvic fibrosis has been thought to be problematic if resection is delayed beyond 6 to 8 weeks.[58–60] However, increasing data suggest that a longer interval between radiation and resection may be beneficial. One study showed improved tumor downstaging if surgery was performed 6 to 8 weeks after radiation compared with 2 weeks after

radiation.[58] A retrospective analysis also suggested an improvement in pCR rates and a decrease in morbidity when surgery was performed greater than 7 weeks after CRT.[59] There has been concern that a longer interval between CRT and surgery could lead to increased operative morbidity and prolonged hospital stays even despite improved pCR rates.[60] Moreover, some studies have failed to demonstrate an association between an increased interval before surgery and improved pCR rates.[61] Nevertheless, with modern surgical care and more refined radiation therapy methods, the emerging data appear to demonstrate the potential to improve pCR by increasing the interval between CRT and surgery. In this vein, there are two trials, the Timing trial and the CONTRE trial, which prolong the duration before surgery by additional pre-operative FOLFOX chemotherapy. The *Timing of Rectal Cancer Response to Chemoradiation Consortium* has just completed accrual. This phase II multicenter trial increased the duration of time between completion of radiation and surgical resection, with placement of some of the adjuvant chemotherapy in the pre-operative waiting period. The trial was designed as a sequential cohort trial, starting with the standard interval between completion of CRT and surgery. Three subsequent cohorts added FOLFOX after 5-FU/RT incrementally (two cycles, four cycles, six cycles) prior to surgical resection, with the primary endpoint being an improvement in pCR. After surgery, additional chemotherapy was delivered for a total of 6 months systemic therapy. This study found that adding two or four cycles of FOLFOX after CRT increased the pCR rates to 25 % and 30 %, respectively, compared with CRT alone (18 %). Importantly, the addition of pre-operative chemotherapy did not increase the rate of adverse events or surgical complications, and over 70 % of patients completed chemotherapy without interruption.[62] The last cohort, which delivered six cycles of pre-operative FOLFOX, has closed to accrual and data will soon be forthcoming. However, preliminary results suggest an even further improvement in pCR rates (personal communication). Despite these improvements in local control, further follow-up is needed. There are two unanswered questions from this trial: not knowing whether the delay in surgical treatment will increase the risk of metastatic disease and not knowing if interrupting FOLFOX chemotherapy will reduce its effectiveness.

An alternative method to maximize pre-operative FOLFOX chemotherapy is being employed in the CONTRE trial. Patients receive eight cycles of upfront FOLFOX chemotherapy, followed by combined modality therapy with 5-FU/RT, followed by surgery. Preliminary data presented at the Gastrointestinal American Society of Clinical Oncology (GI ASCO) 2013 meeting from the first 32 patients reported a 33 % pCR rate with over a 90 % treatment compliance rate.[63] The mature study results from both the Timing Trial and the CONTRE trial are eagerly awaited, and will no doubt provide important information for the design and conduct of future neo-adjuvant rectal cancer trials.

Need for Surgery in All Rectal Cancer Patients?

The possibility of omission of surgery after successful chemoradiation ('organ preservation') is the most pressing current research question in rectal cancer. With most series showing pCR rates of 15–18 %, and newer series showing pCR rates of over 30 %, there may be a subset of patients who will likely not benefit from resection. Several reports have observed that a subset of patients who receive CRT and achieve a clinical complete response (cCR) can have prolonged disease-free intervals without surgery. Habr-Gama reported on a group of 265 rectal cancer patients who received pre-operative 5-FU/RT of which 26 % had a cCR.[64] Patients without a cCR

underwent surgery, while those with a cCR were observed with a monthly digital rectal exam, carcinoembryonic antigen (CEA), proctoscopy with biopsy of any suspicious areas, and an every 6-month abdominal/pelvic CT scan. No adjuvant chemotherapy was administered in this study. Of the 71 patients with a cCR that were observed, there was a 7 % relapse rate but no cancer-related deaths. Interestingly, when compared with patients who had an incomplete clinical response that went to surgery and were found to have a pCR, patients with a cCR who were observed without surgery had similar excellent long-term outcomes.[64,65] Consistent with these findings, a small pilot study prospectively utilized a 'wait and see' approach in patients with a cCR defined by MRI and endoscopy plus biopsies. Strict follow-up criteria was employed every 3 to 6 months with MRI scans, endoscopy, and CT scans. At a mean follow-up period of 25±19 months, only one patient had a documented local recurrence and was salvaged with surgical resection. Compared with a control group who had a pCR after surgery, nonoperative management demonstrated similar disease-free and overall survival.[66] A retrospective review at the Memorial Sloan-Kettering Cancer Center evaluated 32 patients with a cCR after CRT defined by a digital rectal exam and endoscopy. Compared with a group of patients demonstrating pCR at the time of resection, there was no difference in 2-year distant disease-free survival or overall survival. Patients that recurred locally were salvaged with resection; although three patients recurred with distant metastatic disease.[67] While all of these studies pose fascinating and important clinical questions, they will need to be confirmed with larger, randomized phase III trials.

Despite the obvious attraction of identifying patients who could undergo nonoperative management of rectal cancer, there remain critical barriers to overcome before such an approach can be widely adopted. One area of uncertainty is the accurate identification of a cCR. Prior studies have shown discordance between cCR and pCR.[68] Indeed, a complete response in the primary tumor may not be indicative of a complete response in nodal disease. In one series, 7 % of patients with a pCR in the primary tumor had positive nodal disease.[69] This underscores the need for a robust, clear, and precise definition for a cCR. Some investigators have advocated that a cCR can only be documented with a negative full thickness biopsy and normal endoscopic evaluation.[70] However, even such careful approaches can be confounded by operator variability and sampling bias. Other techniques are being investigated to better define a cCR including endorectal ultrasound as well as diffusion-weighted MRI (DW-MRI). A prospective study from 2007 to 2010 showed that DW-MRI can accurately predict pCRs, although

not unequivocally in all circumstances.[71] Retrospective studies have also suggested the utility of DW-MRI in assessing pCR.[72–75] The CARTS study is attempting to define a role for nonradical surgery and incorporates transanal endoscopic microsurgery (TEM) in well-defined patient subsets.[76] More research needs to be carried out to determine the best methods for assessing complete response after neo-adjuvant therapy.

The future of rectal cancer treatment will likely involve more individually tailored therapy. There is a wide spectrum of disease behavior from indolent to more aggressive tumors. Current understanding of biologic markers of disease status in rectal cancer is improving rapidly, with both prognostic and possibly therapeutic implications. The ability to tailor therapy to a patient's disease biology will help optimize treatment. At this time, the rectal cancer field awaits ongoing studies looking to optimize pre-operative therapy by adding additional chemotherapy,[62,63] eliminating radiation,[56,57] or more dramatically, by forgoing surgical resection.[64,66,67,70] Trials which examine the principle of organ preservation are underway including the *Timing and Deferral of Rectal Surgery Following a Continued Complete Response to Pre-operative Chemoradiotherapy*, which is being coordinated by the Royal Marsden GI Clinical Trials Unit.[77] Similar trials have been proposed in the US. However, without better prognostic and predictive biomarkers and more accurate clinical assessment of response to therapy, it will be challenging to prospectively identify which patient subgroups would be appropriate candidates for organ preservation. Thus, without better risk-stratification, definitive phase III clinical trials will be a difficult undertaking given the large sample sizes required and the potential reluctance in recruiting patients to an observation arm. Nevertheless, patients frequently express a strong desire to avoid surgery.[66] Therefore, the research community should not be dissuaded in efforts to launch large randomized clinical trials that include an observation arm after a cCR—as long as robust basic, translational, and clinical endpoints are mandated. For perspective, it is worth noting that anal cancer, which was once a purely surgical disease, is now routinely managed with CRT.[78]

In summary, the integration of multi-modal rectal cancer treatment, improvements in our understanding of the optimal timing of each, and refinements in each mode of therapy have led to substantial improvements in rectal cancer survival. However, there is still much work to be performed to determine the optimal way to integrate these therapies, minimize toxicities, and possibly even provide an organ-preservation approach. ∎

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