Locally Advanced Rectal Adenocarcinoma: Treatment Sequences, Intensification, and Rectal Organ Preservation

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Case Presentation

L.B. is a 68-year-old Hispanic man who presented with hematochezia, narrowed stools, and unintentional weight loss over 4 months. A colonoscopy in May 2019 revealed a 6-cm, nonobstructing, fungating rectal mass 8 cm from the anal verge. Biopsy confirmed a moderately differentiated, invasive adenocarcinoma. Cross-sectional computed tomography (CT) and abdominal magnetic resonance imaging (MRI) did not show apparent metastatic disease, except for benign cysts in the liver. Subsequent MRI with rectal protocol showed a clinical T3N1 (cT3cN1, 8th edition American Joint Committee on Cancer [AJCC]) tumor with extramural vascular invasion and nonthreatened mesorectal fascia. The carcinoembryonic antigen (CEA) level was 38 ng/mL at the time of diagnosis.

L.B. started neoadjuvant modified folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6) in July 2019 and completed 8 cycles without dose reduction or delay. His rectal bleeding improved significantly, and stool caliber normalized after 2 cycles of neoadjuvant induction chemotherapy (INCT). Two weeks after completion of INCT in November 2019, restaging rectal MRI demonstrated a radiographic near complete response (CR) with resolution of pathologic lymph nodes and extramural vascular invasion. The CEA level decreased to 7.6 ng/mL yet remained elevated. Endoscopic evaluation showed an erythematous scar with slight mucosal irregularity and nodularity, consistent with partial treatment effect (Fig. 1).

L.B. then proceeded with long-course chemoradiation (CRT) with capecitabine, which he completed in December 2019. Restaging CT did not demonstrate distant metastatic disease. His CEA level normalized to 4.7 ng/mL, but rectal MRI interpreted residual viable disease T1/T2N0, with persistent, intermediate T2 signal as well as a high signal on diffusion-weighted imaging (DWI). Endoscopically, he had a scar with telangiectasia and decreased mucosal erythema but persistent, subtle, pale mucosal nodules. Given the excellent treatment response to total neoadjuvant therapy (TNT), a short-interval reassessment from completion of TNT was planned to evaluate whether an additional interval of time would result in a clinical CR (cCR), so that a watch-and-wait (WW) approach might be considered. A repeated rectal MRI 10 weeks after completion of TNT again showed an intermediate T2 signal, radiographically consistent with persistent, viable tumor. However, endoscopic evaluation now showed a flat, white scar with telangiectasia and was consistent with a cCR.

Given the discordance between MRI and endoscopy findings, a radical rectal resection was pursued. The patient and family expressed their understanding that there was a moderately high likelihood that no residual disease would be found in the resected specimen; however, they wished to proceed with the operation. He underwent a robotic low anterior resection with diverting loop ileostomy in April 2020, with final pathology demonstrating no residual adenocarcinoma, a pathologic CR (pCR) (negative pathologic tumor and lymph node status [ypT0ypN0]). His recovery was unremarkable and thus he

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underwent ileostomy reversal in June 2020. He is currently under surveillance with normal CEA and no radiographic evidence of disease. He experiences urgency and clustering of bowel movements, consistent with low anterior resection syndrome.

Background

Multimodality therapy for nonmetastatic, resectable, locally advanced rectal adenocarcinoma (LARC) has been routinely administered since the late 1990s, successfully prolonging survival and decreasing local pelvic failure. More recently, the one-size-fits-all treatment paradigm has been scrutinized, with the understanding that tumor downstaging to neoadjuvant therapies correlates strongly with long-term oncologic outcome. The risk of local recurrence now remains marginal relative to the more common and fixed rate of distant failure, such that efforts to tailor therapy play an increasing role in selecting optimal treatment strategies. Treatment approaches have rapidly evolved over the past decade, creating multiple treatment options for patients and physicians alike among clinical stage II (T3-T4, N0) and stage III (Tany, N1-N2) rectal adenocarcinoma (Table 1).1-7

Contemporary prospective trials are studying the main patterns of disease recurrence, long-term mortality, and distant metastasis (DM) as well as realigning the balance between cure and quality of life. To this end, rectal organ preservation (WW) is a promising and increasingly important part of patient care and an area of intense research efforts. Among the treatment considerations for our patient, he expressed a strong interest in rectal organ preservation and wished to maximize his neoadjuvant therapy with the hope of achieving a cCR to potentially avoid or defer rectal resection.

Historical Treatment Paradigm

With optimal total mesorectal excision (TME) surgery and fluoropyrimidine-based, neoadjuvant CRT, patients with LARC experience excellent local control. The rate of DM after curative-intent resection, however, has remained high and stable over the past 2 decades. The landmark German rectal cancer trial (2004) established trimodality treatment with CRT followed by TME and adjuvant chemotherapy (ACT) as the standard of care for LARC in North America.1

The German trial shifted the delivery of postoperative CRT to the preoperative setting and reported an improved therapeutic ratio when given preoperatively. Neoadjuvant CRT significantly decreased treatment-related toxicities (acute, 27% vs 40%; late, 14% vs 24%) and the 10-year local recurrence rate (7% vs 10%) while also increasing sphincter-preservation rates.
ACT delivery based on pathologic results and tumor routine use remains an unresolved controversy. Adaptive rectal cancer after neoadjuvant CRT and TME, and its neoadjuvant therapy; WW, watch and wait. SRT, short-course radiation; TME, total mesorectal excision; TNT, total consolidation chemotherapy; CRT, chemoradiation; CT, chemotherapy; metastatic disease.9 However, there are limited data regimen, with the intended goal of eradicating micro-
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Several randomized trials have specifically evaluated the role of ACT in patients with rectal cancer; however, most suffer from significant limitations, including variability in radiation, chemotherapy regimens, and adherence to intended therapy.13-17 Despite these shortcomings, the data collectively have not demonstrated a survival benefit or improvement in disease-free survival (DFS) for patients who received neoadjuvant (C)RT and subsequently were treated with ACT compared with observation. Two notable exceptions deserve mention; however, the phase 2 Adjuvant Oxaliplatin in Rectal Cancer (ADORE) trial (ClinicalTrials.gov identifier NCT00807911) and the German CAO/ARO/AIO-04 trial (ClinicalTrials.gov identifier NCT00349076) both reported a survival benefit of oxaliplatin-based ACT.18,19 The ADORE trial randomly assigned high-risk patients, based on pathology, who received neoadjuvant CRT (ypT3-ypT4 or ypN-positive) to either 5-FU and leucovorin or folinic acid, fluorouracil, and oxaliplatin (FOLFOX) for 4 months. Six-year DFS was improved in the FOLFOX group (68% vs 57%; hazard ratio [HR], 0.63; 95% CI, 0.43-0.92); however, this benefit was only apparent among patients who had pathologic stage III disease, not pathologic stage II disease.20 Although DFS was statistically improved, OS at 6 years was not different (78% vs 76%; P = .2), suggesting that only certain patient subgroups may derive benefit from adjuvant oxaliplatin-based ACT. The CAO/ARO/AIO-04 trial similarly reported improved 3-year DFS (75.9% vs 71.2%) in patients who received oxaliplatin as a radiosensitizer with neoadjuvant fluoropyrimidine-based CRT as well as in combination adjuvant 5-FU therapies.

Whether ACT should be given to all, none, or specific subsets of patients after CRT and TME is an ongoing debate.17 In addition to this consideration, the optimal duration and timing of chemotherapy is not entirely clear. Traditionally, 2 months of 5-FU–based chemotherapy administered with radiation followed by a 4-month course of adjuvant FOLFOX is considered cumulatively 6 months of chemotherapy and a complete treatment course. This duration of therapy is an extrapolation from the MOSAIC trial, from which 6 months of FOLFOX emerged as the standard for lymph node-positive colon cancer. It should be recognized that 12.5% of patients receiving FOLFOX in the MOSAIC trial experienced long-term grade 3 peripheral sensory neuropathy from 6 months of oxaliplatin-based chemotherapy. Recently, a shorter duration of adjuvant therapy in colon cancer has been studied within the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration, with the primary aim of reducing morbidity while not sacrificing oncologic outcome.21 On the basis of favorable results demonstrating the noninferiority of 3 months of capecitabine plus oxaliplatin in patients with T3N1 colon cancer, it is plausible that rectal cancer chemotherapy treatment duration may be affected in the coming years. Although the above data are partly limited because of study design and extrapolation from colon cancer populations, fluoropyrimidine-based ACT in combination with oxaliplatin remains the current standard of care for most patients in the United States.

### Medical Oncologist Perspective

#### Chemotherapy and sequence of chemotherapy (neoadjuvant vs adjuvant)

In the United States, ACT remains a component of the guideline-recommended trimodality LARC treatment regimen, with the intended goal of eradicating micrometastatic disease.9 However, there are limited data supporting the current guideline recommendation for ACT for all patients who have clinically staged II and III rectal cancer after neoadjuvant CRT and TME, and its routine use remains an unresolved controversy. Adaptive ACT delivery based on pathologic results and tumor responsiveness to neoadjuvant CRT is not the current standard of care, although this may be a preferable approach, restricting chemotherapy to those patients most likely to benefit. In fact, the application of ACT for patients with LARC is largely extrapolated from the benefit reported in large trials evaluating 5-fluorouracil (5-FU) and oxaliplatin in lymph node-positive colon cancers, specifically, the MOSAIC (ClinicalTrials.gov identifier NCT00275210), National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 (ClinicalTrials.gov identifier NCT00004931), and QUASAR (International Clinical Trial Registry Number ISRCTN82375386) trials.10-15

### TABLE 1. Variations in Treatment Sequence Approaches for Locally Advanced Rectal Adenocarcinoma

| TRIAL | SEQUENCE |
|-------|----------|
| Historical, standard, long-course CRT (Sauer 2004) | CRT → TME → ACT |
| Historical, standard SRT (Kapiteijn 2001) | SRT → TME → ACT |
| Total neoadjuvant therapy with long-course CRT (Garcia-Aguilar 2020) | CRT → TME → ACT |
| 1. Induction CT | INCT → CRT → TME |
| 2. Consolidation CT | CRT → CCT → TME |
| TNT with SRT (Hospers 2020) | SRT → CCT → TME |
| Neoadjuvant CT with selective neoadjuvant CRT (Alliance for Clinical Trials in Oncology 2020) | CT → +/- CRT → TME → ACT |
| TNT with WW (Garcia-Aguilar 2020, Hospers 2020, Conroy 2020, Rodel 2020) | INCT → CRT → WW → CRT → CCT → WW |
| TNT with WW (Garcia-Aguilar 2020, Hospers 2020, Conroy 2020, Rodel 2020) | CRT → CCT → WW |

Abbreviations: +/-, with or without; ACT, adjuvant chemotherapy; CCT, consolidation chemotherapy; CRT, chemoradiation; CT, chemotherapy; SRT, short-course radiation; TME, total mesorectal excision; TNT, total neoadjuvant therapy; WW, watch and wait.

Despite improved local disease control with neoadjuvant CRT, the 10-year DM rate was 30% in both arms along with similar 10-year overall survival (OS).8
An important but often under-recognized data point within many rectal cancer trials is the low tolerance and compliance rates of ACT. It is possible that the lack of clear survival benefit may be caused in part by the poor receipt of the intended systemic chemotherapy regimen. In the European Organization for Research and Treatment of Cancer (EORTC) 22921 trial (ClinicalTrials.gov identifier NCT00002523), 57% of patients did not receive or complete the full intended course of ACT.\textsuperscript{22} Similar data have supported poor compliance rates of ACT, including a Surveillance, Epidemiology, and End Results study reporting that only 61% of patients received any postoperative chemotherapy.\textsuperscript{23} For Mr. L.B., this issue of treatment compliance was strongly considered and contributed to our preference to administer neoadjuvant chemotherapy.

**Evolution of treatment paradigms with total neoadjuvant therapy (induction vs consolidation chemotherapy)**

INCT possesses several theoretical advantages and is currently an accepted treatment strategy outlined within the National Comprehensive Cancer Network (NCCN).\textsuperscript{24} Earlier administration of cytotoxic chemotherapy has the potential to eradicate occult micrometastases with intact tumor vascularity in a more fit patient, before a surgical physiologic insult. In addition, the receipt of intended chemotherapy is improved and compliance to subsequent CRT has not been shown to be compromised.\textsuperscript{25,26} The response to chemotherapy may also help define good or bad prognostic groups and predict the response to radiation. Conversely, INCT delays radiative and definitive surgical resection, possibly selecting for radioresistant tumor cell clones.\textsuperscript{27} Apart from these theoretical considerations, the effects of INCT tumor downsizing and downstaging appear at least additive to CRT, increasing the pCR rate significantly and potentially expanding the proportion of eligible patients for rectal organ preservation/WW.

Consolidation chemotherapy (CCT), delivered after (CRT) but before surgical resection, may result in partially damaged but surviving, proliferating tumor cells with increased sensitivity to cytotoxic chemotherapy, thereby preventing tumor repopulation and improving outcomes. The CCT paradigm delivers active treatment throughout a time interval after receipt of CRT. The effects of extended time intervals on downstaging after the completion of CRT are well recognized and of significant importance when rectal organ preservation remains a high priority.\textsuperscript{28-32} Similar to INCT, CCT increases the rates of cCR and pCR, although a direct correlation with improved DFS and OS is not yet certain.\textsuperscript{33,34} In line with the NCCN, we elected to pursue INCT for L.B., intending to maximize both treatment response and treatment compliance.

Several randomized trials have provided insight into TNT,\textsuperscript{35-38} some of which have been recently reported in abstract form.\textsuperscript{3,4,6,39} Overall, the data reflect superior treatment compliance of TNT compared with ACT, increased downstaging with higher pCR rates, and increased rates of rectal organ preservation. Both the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial (ClinicalTrials.gov identifier NCT01558892) and the PRODIGE 23 trial (UNICANCER Gastrointestinal Study 23; ClinicalTrials.gov identifier NCT01804790) demonstrated improvements in DFS and metastasis-free survival (RAPIDO: 3-year DM rate, 20% vs 27%; HR, 0.69; 95% CI, 0.54-0.90; PRODIGE: 3-year DM rate, 21% vs 28%; HR, 0.64; 95% CI, 0.44-0.93) in the TNT arms compared with the CRT-alone arms, potentially moving the needle on the previously stable rate of distant failure. Notably, the 3-year DM rate in those trials did not yet translate into an OS benefit between arms (RAPIDO, 89% vs 89%; PRODIGE, 91% vs 88%; P = .08).\textsuperscript{4} The interim analysis from the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial (ClinicalTrials.gov identifier NCT02008656), directly comparing INCT with CCT and including a WW arm for clinical complete responders, showed a higher 3-year rectal organ-preservation rate within the CCT arm (58% vs 43%; P = .01).\textsuperscript{3} The 3-year DFS and metastasis-free survival rates, however, were not different between the INCT and CCT arms (3-year DFS rate with INCT, 78% vs 77%; 3-year distant metastasis-free survival rate with INCT, 81% vs 83%) (Table 2).\textsuperscript{3,4,6,8,40} The randomized CAO/ARO/AIO-12 trial (ClinicalTrials.gov identifier NCT02363374) comparing INCT versus CCT, which was published in 2019, reported a numerically higher pCR rate in the CCT arm (25% vs 17%).\textsuperscript{41} Whether the addition of systemic chemotherapy in the neoadjuvant setting will translate into improved OS remains unanswered and will require longer follow-up; however, it is clear that the rate of pCR increases consistently and likely provides increased organ preservation for a significant proportion of patients with LARC. In fact, several TNT trials designed to maximize rectal organ preservation with an option of local excision based on tumor response are actively enrolling patients.\textsuperscript{7,42,43}

**Neoadjuvant chemotherapy therapy alone (omitting pelvic radiation)**

Although pelvic radiation reduces local recurrence after TME, it is associated with acute early and late toxicity, including bowel and genitourinary dysfunction, loss of fertility in young patients, and diminished bone marrow reserve with diminished ability to receive subsequent myelosuppressive therapy in the event of distant metastatic disease. In addition, neoadjuvant radiation may result in overtreatment for some patients who might otherwise obtain good tumor control with a meticulous TME, underscoring the importance of proper surgical technique. Although our patient did not have a threatened radial (mesorectal) margin on MRI, he had extramural vascular invasion and invasion beyond the muscularis propria into the mesorectal fat of 10 mm (T3c), both of which are risk factors for increased local and distant failure, such that pelvic radiation was considered necessary.

In a single-institution trial from Memorial Sloan Kettering Cancer Center, 32 patients, including 22 with
clinical lymph node-positive disease, were treated with neoadjuvant FOLFOX (and 4 cycles of bevacizumab). Thirty patients completed neoadjuvant chemotherapy and subsequently underwent an R0 (negative margin) TME. Eight of those 30 patients had a pCR (25%), and 3 patients experienced recurrences, all of which were pulmonary metastases without local recurrence. This study provided the framework for selective, rather than reflexive, radiation based on response to 6 cycles of induction FOLFOX (without bevacizumab). The PROSPECT N1048 trial (ClinicalTrials.gov identifier NCT01515787) seeks to determine whether neoadjuvant FOLFOX alone can safely be delivered without compromising either the ability to perform a negative margin rectal resection or negatively impact local control or DFS for patients who are considered candidates for sphincter-sparing surgical resection at baseline with clinical stage T2N1, T3N0, or T3N1 disease and without a threatened mesorectal fascia margin based on MRI. It is important to recognize that this study includes only lower risk patients with rectal cancer, excluding those with clinical T4 and N2 disease. The Chinese FOWARC trial (ClinicalTrials.gov identifier NCT01211210) recently demonstrated that patients who received 4 to 6 cycles of neoadjuvant FOLFOX without radiotherapy had a lower pCR rate and a higher rate of pathologic lymph node metastases than patients who received pelvic radiation, although both groups had a similar rate of R0 resection. However, the rate of postoperative complications was significantly lower among patients who did not receive pelvic radiation, and downstaging was still observed in 36% of patients.

### TABLE 2. Selected Randomized Clinical Trials and Outcomes

| TRIAL | OUTCOME, % |
|-------|------------|
|       | 10-y DM    | 10-y LF | 10-y OS | pCR |
| Dutch (Kapiteijn 2001, van Gijn 2011) | SRT and TME | 25.0 | 5.0 | 48.0 | - |
|       | TME alone | 28.0 | 11.0 | 49.0 | - |
|       | P       | .21 | <.0001 | .86 |
| German (Sauer 2004, 2012) | Preoperative CRT → TME → ACT | 29.8 | 7.1 | 59.6 | 8.0 |
|       | TME → postoperative CRT → ACT | 29.6 | 10.1 | 59.9 | - |
|       | P       | .09 | 0.48 | .85 |
| RAPIDO (Hopers 2020) | SRT + chemotherapy (CAPOX x 6 or FOLFOX x 9) → TME (experimental) | 20.0 | 8.7 | 89.1 | 28.4 |
|       | CRT → TME → ACT | 26.8 | 6.0 | 88.8 | 14.3 |
|       | HR [95% CI] | 0.69 [0.54-0.90] | 1.45 [0.93-2.26] | 0.92 [0.67-1.25] |
|       | P       | .005 | .09 | .59 |
| PRODIGE 23 (Conroy 2020) | INCT (FOLFIRINOX x 6 cycles) → CRT → TME → ACT | 21.2 | 75.7 | 90.8 | 27.8 |
|       | CRT → TME → ACT | 28.3 | 68.5 | 87.7 | 12.1 |
|       | HR [95% CI] | 0.64 | 0.68 [0.48-0.97] |
|       | P       | .17 | .03 | .08 |
| OPRA (Garcia-Aguilar 2020) | INCT (FOLFOX x 8 cycles) → CRT → TME or WW | 18.0 | 77.0 | 43.0 | 10.0 |
|       | CRT → CCT (FOLFOX x 8 cycles) → TME or WW | 16.0 | 78.0 | 59.0 | 8.0 |
|       | P       | .83 | .63 | .007 |

Abbreviations: ACT, adjuvant chemotherapy; CAPOX, capecitabine and oxaliplatin; CCT, consolidation chemotherapy; CRT, chemoradiation; DFS, disease-free survival; DM, distant metastasis; FOLFIRINOX, leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; INCT, induction chemotherapy; LF, local failure; OPRA, Organ Preservation in Rectal Adenocarcinoma (ClinicalTrials.gov identifier NCT02008656); OS, overall survival; pCR, pathologic complete response; PRODIGE 23, UNICANCER Gastrointestinal Study 23 (ClinicalTrials.gov identifier NCT01804790); RAPIDO, Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (ClinicalTrials.gov identifier NCT01558921); SRT, short-course radiation; TME, total mesorectal excision; TNT, total neoadjuvant therapy; WW, watch and wait.

aThree-year rectal organ preservation (clinical complete response) and pCR rates may better reflect the true proportion of complete responders.
will better clarify whether radiation can be safely omitted in patients with middle to upper LARCs. This is likely to create new management complexities in the context of maximizing organ preservation, for which neoadjuvant chemotherapy alone may be insufficient.

**Radiation Oncologist Perspective: Neoadjuvant Pelvic Radiation**

Before the landmark German trial established preoperative CRT at 50.4 grays in 25 to 28 fractions as the standard for LARC, earlier randomized trials had shown benefits in OS, DFS, and local control with chemotherapy and radiation delivered postoperatively.\(^\text{46-48}\) Despite the wider availability of high-quality rectal-protocoted MRI, some patients may be over-staged and receive unnecessary CRT. In fact, 18% of patients in the postoperative CRT arm of the German trial (staged with endorectal ultrasound or CT) were pathologically stage I and thus would have been overtreated if randomized to the preoperative CRT arm. The European Society of Medical Oncology (ESMO) clinical practice guidelines stratify (early, intermediate, locally advanced, advanced) rectal tumors by MRI characteristics, including location within the rectum (high, middle, low) and relation to the levator floor, nodal status, extent of T3 penetration through the muscularis propria, status of the mesorectal fascia margin, and the presence of extramural vascular invasion, providing treatment recommendations based on the relative risks of disease recurrence.\(^\text{49}\) These ESMO guidelines recommend that early risk and intermediate-risk rectal tumors preferably should be treated primarily by rectal resection alone in an effort to avoid the toxicity of pelvic irradiation.

There is significant debate regarding the optimal radiation regimen. Although long-course CRT is primarily used in the United States, preoperative short-course radiation (SRT) is a well established alternative, delivered in 5 treatments of 5 grays in a single week without concurrent administration of chemotherapy,\(^\text{7}\) initially reported in the Swedish Rectal Cancer Trial using nonoperative rectal surgery (TME technique was not standard), SRT improved oncologic outcomes and was later confirmed by randomized trials in the context of TME surgery.\(^\text{50}\) The seminal Dutch Rectal Cancer trial showed a relative 50% risk reduction in local recurrences compared with surgery alone (10 years: 5% vs 11%; \(P = .0001\)). OS was not significantly different between the 2 arms across the entire trial; however, among a subset of patients with positive lymph nodes and a negative circumferential radial margin, survival was improved.\(^\text{2,40}\) The Medical Research Council (MRC) CR07 National Cancer Institute of Canada (NCIC) C016 trial similarly reported a local recurrence benefit of neoadjuvant SRT in patients undergoing TME without a clear survival benefit.\(^\text{51}\)

A Cochrane meta-analysis comparing SRT with CRT for stage II and III rectal cancers demonstrated significantly lower rates of local recurrence (odds ratio, 0.39-0.72; \(P < .001\)) in the CRT group compared with the SRT group, although no difference in DFS or OS at 5 years was observed.\(^\text{52}\) Although the preferred neoadjuvant radiation approach is not entirely clear, compared with CRT, SRT is expected to be lower in cost, more convenient for patients, and may improve compliance rates because of lower grade 3 and 4 acute toxicity rates. Two randomized trials have directly compared SRT and long-course CRT: the Polish and Australian (Trans-Tasman Radiation Oncology Group) trials.\(^\text{53,54}\) Although the data from these trials do not clearly indicate superiority of a radiation approach, they clearly confirm greater tumor downstaging with a far higher pCR rate in the CRT group. Rates of negative margin resection and sphincter preservation, particularly in patients with a threatened circumferential radial margin, would be expected to increase from the downsizing and downstaging effects obtained with CRT. In addition, the prospect of a pCR allows an opportunity to expand rectal organ preservation in well selected patients.

Understanding the importance of a time interval between receipt of radiation and extent of tumor downstaging, the Stockholm III trial randomized patients to SRT and TME 1 week later, SRT and TME 4 to 8 weeks later, as well as long-course radiation (without chemotherapy) followed by TME 4 weeks later, with local recurrence as the primary endpoint. After a follow-up \(\geq 2\) years, no differences in local or distant recurrences or OS among the regimens was demonstrated; however, postoperative complications were significantly reduced by delaying surgery. Because a delay after delivery of radiation appears to be beneficial, this interval waiting period presents an opportunity to deliver neoadjuvant chemotherapy using a consolidative approach. The recently reported RAPIDO (ClinicalTrials.gov identifier NCT01555921) and Polish II (ClinicalTrials.gov identifier NCT00833131) trials used this strategy, randomizing patients either to SRT, followed by CCT, followed by TME or to the historical standard of neoadjuvant CRT followed by TME. Although these trials cannot directly comment on the superiority of SRT versus long-course CRT, they do help clarify the safety and efficacy of SRT with a delay until surgery.\(^\text{55}\)

**Medical and Radiation Oncologist Perspective: Radiosensitizers**

Multiple radiosensitizing agents have been studied in the neoadjuvant setting to accompany radiotherapy, with 5-FU the primary drug administered. Concurrent chemotherapy potentially enhances the effect of radiation by decreasing tumor cell repopulation. By combining chemotherapy agents with radiotherapy in an adjuvant setting, radiosensitizers reduced the rates of local recurrence in randomized trials conducted in the 1980s and early 1990s.\(^\text{47,56,57}\) After the German trial established the superiority of neoadjuvant CRT, 2 randomized trials subsequently compared preoperative CRT with preoperative long-course radiation without a radiosensitizer.\(^\text{22,58,59}\) Both the EORTC 22921 trial and the Federation Francophone de Cancerologie Digestive
5-FU, which was administered to our patient. Multiple trials have evaluated additional radiosensitizers to use in combination with 5-FU. Among these drugs, oxaliplatin has been most rigorously studied. Three randomized trials have shown increased toxicity with no improvement in response or therapeutic benefit, such that oxaliplatin is not routinely included in current regimens. Multiple trials have evaluated additional radiosensitizers to use in combination with 5-FU. Among these drugs, oxaliplatin has been most rigorously studied. Three randomized trials have shown increased toxicity with no improvement in response or therapeutic benefit, such that oxaliplatin is not routinely included in current regimens. The CAO/ARO/AIO-04 trial, however, did report an increased pCR rate with the inclusion of oxaliplatin to 5-FU–based CRT without added toxicity.

The currently enrolling, phase 2 NRG Oncology trial NRG-GI002 is sequentially enrolling candidate radiosensitizers in the context of a TNT approach. The first completed arm with combination capecitabine and the experimental radiosensitizing drug veliparib, a PARP inhibitor, did not reach the primary endpoint of the trial; however, there was a 20% relative risk reduction in DFS and a 4% absolute OS improvement.

**Surgical Oncologist Perspective**

**Timing of surgery**

Even considering recent advances in neoadjuvant treatment strategies, cure is unlikely without surgical resection. TME—sharp dissection along the embryologic planes—removes residual nodal and/or tumor deposits within the draining mesorectal lymphatic drainage. An incomplete TME results in remnant mesorectal tissue, potentially harboring viable disease, and partially accounts for pelvic local recurrences. Regarding surgical timing, TME has been typically recommended to occur within 1 week of receipt of SRT or within 6 to 8 weeks after CRT, mostly because of fears of surgical morbidity secondary to the effects of radiation, including radiation-induced pelvic fibrosis. The GRECCAR6 trial (ClinicalTrials.gov identifier NCT01648894) reported that an 11-week interval, compared with a 7-week interval, after receipt of CRT was associated with higher postoperative morbidity. In contrast, other large series have not shown an association of time interval and surgical complications, such that an extended interval before surgery is acceptable.

Our current understanding allows a more flexible window of surgical resection because we now appreciate that the resected rectal specimen provides only a simple snapshot of a downsizing and downstaging process that may be incomplete. As discussed above, multiple permutations of neoadjuvant sequences may be applied. Although the effects of these variables on patient outcomes is still not fully understood, the importance of a time interval after completion of neoadjuvant treatment is a well recognized factor to maximize tumor downstaging. A retrospective cohort of 2000 patients with LARC reported that a time interval from CRT >13 weeks was associated most with a pCR (31%). This directly impacts the ability to consider a patient for rectal organ preservation, depending on the degree of tumor response, as assessed by restaging MRI, endoscopy, and physical examination. Our patient was reassessed serially after the completion of TNT. Although his last endoscopic evaluation of the extent of tumor response was endoscopically consistent with a cCR, the MRI suggested residual viable disease. Although close observation could have been pursued, this discordance generated patient and family anxiety. This highlights the spectrum of patient preferences and the importance of patient-guided decision making in rectal cancer treatment.

**Nonoperative management/watch and wait**

A complete tumor response (cCR or pCR) is not frequently encountered after TNT and should be considered an unexceptional event. This subset of complete responders has produced many questions revolving around patient selection—primary among these, whether formal radical resection is superfluous. For those patients who have a cCR after neoadjuvant therapy, deferring surgical resection and consequently avoiding significant morbidity without necessarily sacrificing oncologic outcome is an increasingly relevant clinical scenario. These patients achieving a pCR (or a sustained cCR) have lower rates of tumor recurrence and improved survival compared with patients who do not achieve a pCR, creating uncertainties regarding the added value of surgery. For our patient, an excellent oncologic prognosis is anticipated given the confirmation of a pCR.

Despite favorable oncologic outcomes, along with clear quality-of-life benefits secondary to rectal preservation, the primary limitation to a WW approach remains optimal patient selection. This limitation was well demonstrated in the case of L.B. Ideally, a cCR is perfectly concordant with a pCR. Yet the attempt to macroscopically correlate microscopic disease is an imperfect exercise. When using the currently available resources for clinical tumor assessment, including rectal MRI, endoscopy, and clinical examination, some patients with a pCR may not be clinically consistent with a cCR; and, conversely, patients who are considered to have achieved a cCR may actually harbor occult, viable tumor cells in the rectal specimen. Fortunately, growing experience and understanding of postneoadjuvant treatment endoscopic and radiographic tumor response characteristics have improved the ability to accurately classify a patient's tumor response and guide subsequent management. Still, predicting tumor response and optimizing the accuracy, timing, and intervals of response assessment remain unmet needs. As the field advances, ancillary tools, such as sensitive...
biomarkers and radiomics, may enhance the ability not only to predict, but also to determine, the extent of tumor response. Ultimately, the prospect of a cure from neoadjuvant therapies with preservation of the rectum highlights the importance of multidisciplinary collaboration between medical and radiation oncologists, radiologists, surgeons, and, most importantly, the patient.

**Conclusions**

Multidisciplinary teams are essential to care for patients with locally advanced rectal cancer. The treatment paradigm had been stable for many years; however, it is currently in active evolution and is dynamically changing with the addition of recent trial data. The sequences and goals of therapies must be considered within the context of each patient’s presentation and preferences. Historically, most patients received an empirical treatment strategy, with little role for tumor response assessment after neoadjuvant therapy. We have since learned that reflexive, predetermined approaches should be carefully reevaluated, particularly in relation to patients with an apparent CR, such that rectal resection may be selectively avoided or deferred. Still, neoadjuvant CRT followed by TME and ACT remains the most applied approach for LARC. This treatment paradigm is shifting and likely will be replaced with total neoadjuvant strategies or selective pelvic radiation in the near future.

**Disclosures**

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