Commentary: Rectal Cancer—An Evolution of Treatment

BRIAN G. CZITO, CHRISTOPHER G. WILLETT

Radiation Oncology—Clinical Support, Duke University Medical Center, Durham, North Carolina, USA

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The treatment of rectal cancer has evolved substantially over the past two decades. In the past, rectal cancer was frequently treated with surgery alone, which resulted in high rates of local failure, with significant patient morbidity and mortality. Sentinel trials in the 1980s to early 1990s demonstrated that adjuvant chemoradiotherapy resulted in lower rates of local failure and superior survival versus resection alone [1, 2]. This observation led to the adoption of adjuvant chemoradiotherapy as standard treatment for patients with stage II–III disease. Subsequently, proponents of total mesorectal excision (TME) reported that local regional failure rates were <10% with this approach, bringing the role of radiation therapy into question. However, a large, randomized Dutch trial comparing neoadjuvant radiation therapy alone followed by TME with TME alone showed that despite the superior surgical technique, radiation therapy resulted in a significantly lower rate of local failure. The 2-year local failure rate was 2.4% for patients undergoing preoperative radiation therapy and TME versus 8.2% for patients undergoing TME only (p < .001) [3]. The sequencing of radiation therapy relative to surgery has been controversial for several decades. Advocates of preoperative therapy argued that this approach had many benefits, including higher rates of sphincter preservation and better radiation tolerance. In Germany, a large randomized trial (CAO/ARO/AIO-94) comparing preoperative chemoradiotherapy confirmed that a preoperative approach resulted in a significantly lower rate of local failure. The 2-year local failure rate was 2.4% for patients undergoing preoperative radiation therapy and TME versus 8.2% for patients undergoing TME only (p < .001) [3]. The sequencing of radiation therapy relative to surgery has been controversial for several decades. Advocates of preoperative therapy argued that this approach had many benefits, including higher rates of sphincter preservation and better radiation tolerance. In Germany, a large randomized trial (CAO/ARO/AIO-94) comparing preoperative chemoradiotherapy confirmed that a preoperative approach resulted in superior treatment compliance, less acute and late toxicity, and a significantly higher rate of local regional control, again simply by altering the sequence of chemoradiotherapy in relationship to surgery [4]. This has led to a new standard of care in the U.S. and Europe in the treatment of stage II–III and selected stage IV rectal cancer patients.

The primary disadvantage of preoperative chemoradiotherapy is the potential to irradiate patients with stage I (T1-2 N0) disease. When treated with TME alone, these patients have low rates of local recurrence and any benefit of radiation therapy is limited. Therefore, meticulous pretreatment staging with endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) is important. Despite this, there is still the potential to “upstage” patients who have early-stage disease. This is exemplified in the adjuvant arm of the German rectal trial where 18% of patients staged to have stage II or greater disease by EUS preoperatively were found to have pathologic stage I disease [4]. The integration of thin-section MRI into the pretherapy evaluation of rectal cancer patients likely represents a further refinement in staging accuracy and may potentially spare stage I patients from neoadjuvant therapy. In the hands of experienced endoscopists and radiologists, preoperative EUS and MRI appear to strongly correlate with pathologic stage.

As discussed by Drs. Glynne-Jones and Harrison [5], contemporary randomized trials have demonstrated that neoadjuvant chemoradiotherapy produces superior tumor downstaging, pathologic complete response rates, and local control relative to preoperative radiation therapy alone. Therefore, it is logical to assume that, in patients with low-lying rectal cancers, sphincter preservation through downstaging may be achieved in some patients with neoadjuvant therapy, particularly with the knowledge that “historically” large distal margins may not be necessary to obtain durable...
local control. Several trials have suggested that better sphincter preservation is possible with neoadjuvant therapy. The German CAO/ARO/AIO-94 study comparing pre- with postoperative chemoradiotherapy demonstrated a 20% absolute advantage in sphincter preservation in patients initially deemed to require abdominoperineal resection (APR) on subset analysis (39% versus 19%; \( p < .01 \)), despite significantly more low-lying tumors in the preoperative group [4]. This indicates that sufficient downstaging occurred in some neoadjuvantly treated patients to lead to an altered operative approach. The National Surgical Breast and Bowel Project R03 trial of similar design showed a 10% absolute advantage in sphincter preservation with neoadjuvant therapy in disease-free patients (44% versus 34%; \( p \) not stated) [6]. In contrast to these studies, a recent Polish trial comparing short-course preoperative radiation therapy and immediate surgery with long-course preoperative chemoradiotherapy and delayed surgery showed no difference in sphincter preservation rates in patients initially deemed to require APR, despite significant downstaging in patients receiving combined therapy [7]. It should be remembered that sphincter preservation in rectal cancer is not only dependent on variables such as tumor location and individual anatomy, but is also highly dependent on both a surgeon’s skill and willingness to carry out this operation in light of downstaging/initial surgical impressions. Whether preoperative therapy results in better sphincter preservation is a matter of ongoing debate.

Several recent reports of European randomized trials have compared preoperative radiation therapy with or without concurrent chemotherapy [8, 9]. While these trials have shown improvements in local control and response rates with concurrent chemotherapy and radiation therapy, no survival advantage has been observed. This is in contrast to earlier trials comparing adjuvant radiation therapy alone with combined chemoradiation therapy. What has become clear with the contemporary treatment approach of preoperative chemoradiotherapy and TME is that local regional failure has become increasingly uncommon, with most series reporting rates < 10%. The dominant pattern of failure following treatment in rectal cancer is now distant relapse. More recently, the administration of newer chemotherapeutic (capecitabine, oxaliplatin, irinotecan) and targeted (bevacizumab, cetuximab) agents in patients with metastatic colorectal cancer has led to improvements in disease-free and overall survival rates. Therefore, the integration of these agents into the neoadjuvant therapy of rectal cancer is a logical step.

In conclusion, neoadjuvant chemoradiotherapy combined with total mesorectal excision has now become a standard treatment for locally advanced rectal cancer in the U.S. and Europe. With this approach, local regional failure rates should be < 10%. The development of distant metastases is now the predominant mode of failure in this disease, obviating the need for better systemic therapies. Based on the positive data in metastatic colorectal cancer and synergy with radiation therapy in preclinical models, there is a strong rationale to integrate newer generation cytotoxic chemotherapeutics and targeted therapies into the neoadjuvant therapy of rectal cancer. These agents are now being incorporated into the testing of new strategies in this disease, with goals of further enhancing tumor downstaging, local control, metastasis-free survival, as well as long-term survival. Phase I and II studies have been completed evaluating these approaches, and it appears that the combination of these agents with radiation therapy delivered neoadjuvantly can be carried out safely with improved response rates. Ongoing and planned American and European phase III trials will help further determine the tolerability and ultimate efficacy of these agents in this setting.

**References**


