Thirty Years of Rectal Cancer Research: A Brief History

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Prior to the mid-1980s, patients with rectal cancer usually underwent surgery alone, resulting in high rates of pelvic failure with subsequent morbidity and death. Trials from the 1980s to 1990s showed that postoperative chemoradiotherapy decreased pelvic failure rates and improved survival, leading to its incorporation into the routine management of patients with resected stage II/III disease.[1,2] A growing European surgical experience showed that total mesorectal excision (TME) alone resulted in high rates of local control, demonstrating the importance of surgical technique in reducing pelvic failure and raising the question of the need for radiation therapy.[3]

However, a large randomized trial from the Netherlands demonstrated that patients receiving preoperative radiation therapy and TME had significantly lower rates of pelvic relapse vs patients undergoing TME only.[4] Follow-up analyses of this trial have further shown that node-positive patients undergoing TME alone experience pelvic failure rates exceeding 20%.[5] More recently, the German Rectal Cancer Study demonstrated that preoperative chemoradiotherapy (vs postoperative therapy) leads to superior pelvic control and sphincter preservation, as well as lower rates of acute and chronic toxicity.

Based on these study results, a new standard of care in the United States and Europe now exists for patients with clinical stage II/III and selected stage IV rectal cancer patients.[6] Other European trials have recently established the value of concurrent chemotherapy with preoperative radiation therapy in optimizing local disease control.[7,8] Using the approach of preoperative chemoradiotherapy and TME, pelvic failure rates are now less than 10%. So where do we go from here?

Newer Chemoradiotherapy Regimens

With the decreasing rates of local failure using contemporary techniques, the dominant pattern of failure in rectal cancer is now systemic. Because newer chemotherapeutic/targeted agents (capecitabine [Xeloda], oxaliplatin [Eloxatin], bevacizumab [Avastin], cetuximab [Erbitux], panitumumab [Vectibix]) have improved outcomes in patients with metastatic disease, the incorporation of these agents into a neoadjuvant combined-modality approach to rectal cancer is logical. However, the integration of these agents will also undoubtedly result in increased acute and chronic toxicities.

Nonetheless, the rationale behind novel combined regimens is multifold: (1) patients receive systemic therapies early in the course of treatment where there may be a lesser burden of disease and better drug perfusion in a nonsurgically manipulated tumor; and (2) these agents are radiosensitizers, potentially leading to enhanced rates of downstaging and pathologic complete response. Phase I and II studies have evaluated these approaches, and it appears that a combination of most of these agents with radiation therapy in a neoadjuvant setting can be accomplished safely with improved pathologic response rates.[9] Regarding improved downstaging and pathologic response rates, one could ask the question, “Does it really matter?” given the existing high rates of local-regional control. Arguably, the answer is yes on two fronts.

First, improved tumor downstaging may lead to enhanced rates of sphincter preservation, particularly in lower rectal cancers. As described by Drs. Minsky and Guillem, data from the German Rectal Cancer Trial as well as the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial evaluating pre- vs postoperative therapy suggest that a preoperative approach results in significantly improved rates of sphincter preservation in patients initially deemed to require abdominoperineal resection.[6,10] In contrast, Polish trial results comparing short-course preoperative radiation therapy to long-course preoperative combined-modality therapy showed no difference in sphincter preservation.[11] However, sphincter preservation depends on many variables, including tumor location, individual anatomy, the surgeon’s technical skills, and his or her willingness to change the operative approach in light of downstaging. Improved downstaging could potentially enhance these rates.
Second, many reports have shown that patients achieving improved pathologic response rates with neoadjuvant therapy have superior outcomes compared to those with residual disease. Analysis of neoadjuvantly treated patients from the German Rectal Cancer Study showed an increasing histologic response predicted for long-term disease-free survival.[12] Similarly, a recent European collective experience evaluated over 500 patients achieving pathologic complete response following neoadjuvant therapy.[13] Only 22% of patients received adjuvant chemotherapy. Locoregional recurrence was seen in < 2% of patients, and distant metastases in only 9%, resulting in impressive 5-year actuarial disease-free and overall survival rates of 85% and 90%, respectively. Whether locoregional response predicts systemic response remains unknown. However, given the favorable results in patients achieving an improved histologic response, integrating newer agents with radiation therapy in efforts to improve ultimate outcomes is appropriate.

**Two Key Questions**

Do all patients with rectal cancer require surgery after “neoadjuvant” therapy, and do all patients require radiation therapy? The answer to both questions is probably not. Habr-Gama and colleagues published intriguing data from an evaluation of 361 patients with distal rectal cancer treated with neoadjuvant chemoradiotherapy. Approximately one-third of patients achieved a complete clinical response and were followed without operation. Approximately 80% of this group maintained a complete response 1 year following the completion of therapy and continued to be managed nonoperatively. At a mean follow-up of 5 years, the local failure rate in nonoperative patients was 6%, with the majority of local failures undergoing successful surgical salvage.[14]

However, as discussed by Drs. Minsky and Guillem, the difficulties in this approach include the fact that, presently, there are no reliable predictors for patients achieving a pathologic complete response to neoadjuvant therapy, pelvic recurrences may be difficult to detect and/or salvage, and relapses may occur many years posttreatment—even beyond 5 years. Additionally, pathologic complete response rates to multidrug chemoradiotherapy regimens are still roughly one-third at best, indicating that more active regimens are necessary. Nonetheless, a pilot study from the United Kingdom is prospectively investigating a nonoperative approach in locally advanced rectal cancer patients undergoing preoperative chemoradiotherapy. Patients with a complete response as judged clinically and by serial magnetic resonance imaging have surgery deferred, and are instead followed by serial imaging and clinical/endoscopic examination.[15]

In addition to the question of whether surgery is necessary in all patients undergoing neoadjuvant therapy, as discussed by the authors, there are clearly patients who are unlikely to benefit from radiation therapy. As suggested by Drs. Minsky and Guillem, patients with pT3, N0 upper rectal tumors who undergo TME with adequate lymph node sampling and a lack of adverse pathologic features may be appropriate for omission of radiation therapy. However, the quality of surgical resection is critical in such decisions. The standard recommendation that 12 lymph nodes be evaluated for adequate histologic staging is often not achieved, and with the increasing use of neoadjuvant therapy, this may be even more problematic.[16]

**Other Unresolved Issues**

In addition to the above questions—ie, will newer combined regimens result in improvement over fluorouracil/radiation therapy, and which patients can be spared surgery and radiation therapy—other questions remain: What are the fundamental mechanisms underlying the response to chemoradiotherapy synergism, and could integration of “targeted” agents result in unexpected toxicities or an antagonistic effect?[9] Will the integration of novel systemic agents from the metastatic setting translate into gains in the adjuvant setting? Can positron-emission tomography (PET), other imaging modalities, and molecular markers more accurately predict for pathologic complete response and long-term disease-related outcomes? Will the integration of newer radiation technologies including PET-based treatment planning, intensity-modulated radiation therapy, proton therapy, and image-guided radiation therapy decrease acute and long-term complication rates without affecting local control rates, and is safe radiation dose escalation possible with these techniques? Will the identification of molecular prognostic markers allow “customization” of treatments?

These and other questions are current topics of investigation in this disease. While the treatment of rectal cancer has changed significantly over the past 3 decades with a corresponding improvement in patient outcomes, the answers to these and future questions will continue to result in therapeutic trials and evolution.

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