Treating Rectal Cancer: Key Issues Reconsidered

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Minsky and Guillem should be commended for this excellent review and for addressing major areas of controversy in the management of rectal cancer. Among the many issues they cover, the authors review the supporting evidence for the use of neoadjuvant vs adjuvant chemoradiation in patients with stages II/III rectal cancer. They conclude, based on the decreased risk of local recurrence and decreased acute and delayed toxicities, that neoadjuvant chemoradiation should be the preferred standard of care in stage II and III rectal cancer.[1]

The authors proceed to discuss the limitations of ultrasound and magnetic resonance imaging in the clinical staging of rectal cancer, and the limited accuracy of both modalities in lymph node staging. Despite the potential for lymph node overstaging (18%) by endorectal ultrasound and the resulting overtreatment with neoadjuvant chemoradiation, the authors make the case for a neoadjuvant chemoradiation strategy based on the improved local recurrence rates and decreased toxicity with a neoadjuvant modality in the intention-to-treat population on the AIO study.[1]

At Roswell Park Cancer Institute, we certainly agree with this strategy. Indeed, Dr. Guillem had previously reported on a population with uT3, N0 rectal cancer treated with neoadjuvant chemoradiation, with 20% of the patients showing evidence of pathologic lymph node involvement at the time of curative-intent surgery.[2] Given the high risk of clinical lymph node understaging for patients with uT3, N0 disease, the current balance should clearly support a neoadjuvant chemoradiation strategy for all patients with uT3 and/or uN1-2 disease.

pT3, N0 Disease

The authors subsequently discuss the potential overtreatment of the subgroup of patients with proximal pathologic T3, N0 disease. The Dutch study randomized rectal cancer patients to surgery vs 5 × 5 Gy of radiation, followed by surgery. No notable benefit in local relapse was derived in patients with proximal pT3, N0 tumors, suggesting that this group of patients may not benefit from adjuvant chemoradiation in the absence of other poor prognostic factors.[3,4] Based on this finding, the authors suggest that, in this group of patients, the potential improvement of 3% to 4% in local relapse may not be worth the risk.

It should be noted, however, that the German CAO/ARO/AIO 94 trial failed to show a difference in benefit based on tumor location.[1] Furthermore, the lack of reporting on the completeness of total mesorectal excision (a known risk factor for disease recurrence) in US practices makes it difficult to discount chemoradiation in proximal T3, N0 patients at this point. A strategy of chemoradiation elimination may be considered in select patients with proximal T3, N0 tumors with adequate lymph node sampling and without unfavorable tumor characteristics (high-grade, lymphovascular invasion) only if a complete mesorectal excision is confirmed on pathologic examination.

Neoadjuvant Chemotherapy

The authors also discuss chemotherapy status in the treatment of rectal cancer. The standard neoadjuvant chemotherapy is protracted infusional fluorouracil (5-FU) combined with radiation therapy, based on North Central Cancer Treatment Group (NCCTG) 85-47-51. The Intergroup (INT) 0144 trial has demonstrated that 5-FU combined with leucovorin and radiation therapy is equivalent to a regimen of protracted 5-FU-plus-radiation therapy. The authors quote the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) adjuvant study in patients with stage III colon cancer to support the substitution of 5-FU plus capecitabine (Xeloda).[5] It may be as important to note that two large case-control studies have reported favorable results in terms of downstaging when capecitabine was compared to protracted 5-FU or 5-FU/leucovorin concurrently with radiation.[6,7] Therefore, we believe that capecitabine substitution for infusional 5-FU or 5-FU/leucovorin
concurrently with radiation is an acceptable approach. We disagree, however, with regard to the acceptance of 5-FU-plus-oxaliplatin (Eloxatin)-based radiation therapy in the routine chemoradiation of rectal cancer. Whether oxaliplatin is given weekly or every 4 weeks in combination with 5-FU and radiation, excessive gastrointestinal toxicity has been noted.[8,9] Furthermore, given the limited experience with this combination plus radiation therapy and the lack of long-term toxicity data in this setting, it would be premature to implement oxaliplatin/5-FU neoadjuvant chemoradiation outside of a clinical trial setting.

The use of oxaliplatin, capecitabine, and radiation therapy in the neoadjuvant treatment of rectal cancer appears to be associated with similarly increased rates of complete pathologic response and with better tolerability.[10,11] The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 trial will conclusively determine the role of capecitabine, 5-FU, plus oxaliplatin, and capecitabine plus oxaliplatin concurrently with radiation therapy in the neoadjuvant treatment of rectal cancer.

**Adjuvant Chemotherapy**

The authors also address the role of adjuvant chemotherapy in stage II/III rectal cancer following neoadjuvant chemoradiation and surgery. We believe that this is an area of significant controversy. The standard treatment has been, historically, in the form of four cycles of the Mayo clinic 5-FU/leucovorin regimen or two to three cycles of the Roswell Park 5-FU/leucovorin regimen. One may extrapolate from the X-ACT study and consider an alternative of six cycles (4 months) of capecitabine monotherapy.[5]

Although we agree that FOLFOX (continuous-infusion 5-FU, leucovorin, and oxaliplatin) has become a favored regimen compared with fluoropyrimidine monotherapy by extrapolation from the MOSAIC study, we would caution that the duration of treatment with such a regimen in the adjuvant treatment of rectal cancer has not been determined. While the authors report that four cycles are recommended (we believe they meant 4 months), we would argue that the optimal duration is unknown and is somewhere between 8 and 12 cycles (4–6 months).

The rationale for 6 months is based on the MOSAIC study, where 12 cycles of oxaliplatin-based chemotherapy were superior to 12 cycles of 5-FU/leucovorin in stage III colon cancer.[12] Therefore, from a purist standpoint, 12 cycles of FOLFOX may be needed as adjuvant therapy in patients who have received neoadjuvant fluoropyrimidine/radiation therapy followed by resection. A period exceeding 4 months of oxaliplatin-based adjuvant chemotherapy would not be indicated in patients with neoadjuvant oxaliplatin plus fluoropyrimidine-based radiation therapy.

On another note, NSABP C-07 demonstrated similar benefits to MOSAIC in reducing recurrence in patients with stage III colon cancer while using nine doses of oxaliplatin (equivalent to oxaliplatin dosing in nine cycles of FOLFOX).[13] Thus, by extrapolation from this study, the use of 4 months of oxaliplatin-based adjuvant chemotherapy may be sufficient in patients with prior neoadjuvant chemoradiation. Unfortunately, no studies are addressing the duration of oxaliplatin-based chemotherapy in the adjuvant treatment of rectal cancer. Intergroup E5204 has endorsed a total duration of oxaliplatin of 12 cycles in the neoadjuvant/adjuvant treatment of rectal cancer as its standard arm.

The use of capecitabine plus oxaliplatin in the adjuvant setting of rectal cancer is still considered investigational. Awaited results from the AVANT study (not NSABP C-07, as indicated by the authors) will help determine whether we can extrapolate this regimen to use in rectal cancer.

**Surveillance**

Another important issue addressed in this review is the duration of surveillance for disease recurrence in patients with resected rectal cancer. As the authors have pointed out, a 7-year follow-up period is appropriate for rectal cancer patients based on ongoing recurrences beyond 5 years. We argue that similar surveillance approaches may be indicated for colon cancer. Recent data from the MOSAIC study suggest that recurrences beyond 5 years in patients receiving FOLFOX chemotherapy are not uncommon.[14] Therefore, a 7-year surveillance period may be prudent for colorectal cancer and should not be limited to patients with rectal primaries.

**References:**

2. Guillem JG, Diaz-Gonzalez JA, Minsky BD, et al: cT3N0 rectal cancer: Potential overtreatment with...

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