Multidisciplinary Management of Resectable Rectal Cancer

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Prior to the publication of the German CAO/ARO/AIO 94 trial, the conventional adjuvant approach for patients with clinically resectable, ultrasonographically diagnosed T3 (uT3) and/or node-positive rectal cancer was initial surgery and, if pathologically confirmed T3 (pT3) and/or node-positive, postoperative combined chemotherapy plus radiation. The German trial confirmed that compared to postoperative therapy, the preoperative approach was associated with significantly lower local recurrence rates, less acute and chronic toxicity, and an increased incidence of sphincter preservation.

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Clinical Staging

Given this shift to preoperative therapy, clinical staging to accurately identify both T stage and N stage is critical. Imaging techniques to assess the extent of the primary tumor include computed tomography (CT), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose–positron-emission tomography (FDG-PET), and transrectal ultrasound. In the United States, ultrasound plus CT or MRI are commonly used, whereas in many European countries, high-resolution MRI is preferred. High-resolution MRI also allows for identification of patients likely to have close or positive radial margins if they have undergone initial surgery and therefore are selected to receive preoperative therapy. The UK-based Mercury Trial also uses MRI to select for the intensity of preoperative therapy.[2]

The overall accuracy in predicting T stage is approximately 50% to 90% with transrectal ultrasound[3] and 50% to 70% with CT or MRI.[4] FDG-PET may be more accurate than CT for identification of metastatic disease.[5,6] High-resolution MRI is helpful in predicting patients who will have negative margins at surgery. FDG-PET is not as accurate.[7] The identification of positive lymph nodes is more difficult. The overall accuracy in detecting positive pelvic lymph nodes with the above techniques is approximately 50%. The accuracy of MRI is similar to that of CT in this setting; however, it is improved with the use of external and/or endorectal coils. Both CT and MRI can identify lymph nodes measuring ≥ 1 cm, although enlarged lymph nodes are not pathognomonic of tumor involvement. The accuracy of MRI may be further enhanced with the use of superparamagnetic iron oxide particles.[8] Likewise, the accuracy of ultrasound for the detection of involved perirectal lymph nodes may be augmented if combined with fine-needle aspiration.[9]

The ability to accurately predict the pathologic stage following preoperative chemoradiotherapy with MRI,[10,11] ultrasound,[12,13] FDG-PET,[14] or physical exam[15] remains suboptimal. Tumor regression grade[16] may help predict lymph node–positive disease. However, patients in this situation would have already received preoperative chemoradiotherapy.

Is Pelvic Radiation Required for Node-Negative Rectal Cancer?

The 1990 National Cancer Institute (NCI) Consensus Conference recommendation for postoperative combined-modality therapy was based on trials where neither total mesorectal resection (TME) nor examination of ≥ 12 nodes was required. Retrospective data suggest that there may be a subset of patients with pT3, N0 disease who may not require adjuvant therapy. Nissan and associates reported results in 100 patients with uT2/3, N0 disease who underwent TME alone and had at least 12 nodes examined.[17] In the subset of 49 patients with pT3, N0 disease, the overall local recurrence rate...
was 4%. For the total group, local recurrence was significantly higher in those with lymphatic vessel invasion (32% vs 6%, \( P = .006 \)) and an elevated (> 5.0 ng/mL) preoperative carcinoembryonic antigen (21% vs 0%).

The sixth edition of the American Joint Commission on Cancer (AJCC) staging system subdivides stage III into IIIA (T1-2, N1), IIIB (T3-4, N1), and IIIC (T any, N2). The prognostic validity of this change was supported by both the pooled analysis of Intergroup and National Surgical Adjuvant Breast and Bowel Project (NSABP) postoperative trials[18] and the retrospective analysis of the American College of Surgeons National Cancer Database (NCDB).[19] The 5-year survival by stages IIIA, B, and C in the pooled analysis was 81%, 57%, and 49%, and in the NCDB was 55%, 35%, and 25%, respectively.

These data provided further evidence that patients with upper rectal cancers who undergo a TME, have at least 12 nodes examined, and have stage pT3, N0 disease likely do not need the radiation component of chemoradiotherapy. The approximately 3% to 4% benefit in local control with radiation may not be worth the risks, especially in women of reproductive age. However, the subset of patients with pT3, N0 tumors with either adverse pathologic features and/or fewer than 12 nodes examined should still receive postoperative chemoradiotherapy.

Although the appropriate number of nodes is defined in the AJCC staging system, the location of pelvic nodes is not. Leibold and associates treated 121 patients with preoperative chemoradiotherapy and found that the incidence of metastatic disease was higher among patients with positive nodes in the proximal pelvis compared with positive nodes anywhere in the pelvis (46% vs 32%).[20] Of note, the proximal nodes are above the superior border of the radiation field (L5/S1) since they are located along the apical and midportion of the inferior mesenteric artery.

**Potential Overtreatment With Preoperative Therapy**

In the German trial, 18% of patients who were clinically staged as cT3, N0 preoperatively and underwent initial surgery without preoperative therapy had pT1-2, N0 disease. Therefore, those patients would have been overtreated if they had received preoperative therapy. Although it is not ideal, preoperative therapy is still preferred to performing surgery first because even after preoperative chemoradiotherapy (which downstages tumors), 22% will have lymph node–positive disease at the time of surgery.[21] In patients who undergo surgery alone, this number is as high as 40%. These patients will then require postoperative chemoradiotherapy, which, compared with preoperative chemoradiotherapy, has inferior local control, higher acute and chronic toxicity, and if a low anastomosis is performed, inferior functional results. Clearly, the development of more accurate methods to identify lymph node–positive disease including imaging techniques and/or molecular markers is essential as more patients are being treated with preoperative combined-modality therapy.

**Preoperative Short-Course Radiation vs Chemoradiation**

Twelve modern randomized trials of preoperative radiation therapy (without chemotherapy) have been conducted. All use low to moderate doses of radiation. Most of the trials showed a decrease in local recurrence, and in five of the trials this difference reached statistical significance. Although in some trials a subset analysis revealed a significant improvement in survival, the Swedish Rectal Cancer Trial is the only one that reported a survival advantage for the total-treatment population.[22] With 13-year follow-up, survival is still significantly improved (38% vs 30%, \( P = .008 \)) in this group. The local recurrence rate in lymph node–positive patients who underwent surgery alone was 46%, illustrating the inferior results of surgery prior to the adoption of TME.

The updated results of the Dutch CKVO 95-04 trial revealed that 5-year local recurrence with TME is 11% but was still significantly decreased to 6% with preoperative radiation.[23] Furthermore, local recurrence in patients with positive nodes who underwent surgery alone was 21%. Therefore, despite undergoing a TME, node-positive patients still require chemoradiotherapy. The challenge is the identification of positive nodes to allow proper selection of patients for preoperative therapy.

**Sphincter Preservation With Preoperative Radiation**

From the viewpoint of sphincter preservation, the advantage of preoperative therapy is to decrease the volume of the primary tumor. When the tumor is located in close proximity to the upper part of the anorectal sphincter, a decrease in tumor volume may allow the surgeon to perform a sphincter-conserving procedure that would not otherwise be possible. However, if the tumor directly invades the anorectal sphincter, sphincter preservation is unlikely even when a complete response is achieved.

If the degree of downstaging needs to be adequate to enhance sphincter preservation, which regimen (short-course or combined-modality therapy) is preferred? An analysis of 1,316 patients who received a short course of radiation revealed that downstaging was most pronounced when the
interval between the completion of radiation and surgery was at least 10 days.[24] In the Dutch CKVO 95-04 trial, where the interval was 1 week, there was no downstaging.

When the goal of preoperative therapy is sphincter preservation, conventional radiation doses and techniques are recommended. These include multiple-field techniques to a total dose of 45 to 50.4 Gy at 1.8 Gy/fraction. Surgery should be performed 4 to 8 weeks following the completion of radiation. Unlike the intensive short-course radiation regimen, this conventional design allows for two important events to occur. First is the recovery from the acute side effects of radiation, and second is adequate time for tumor downstaging.

Data from the Lyon R90-01 trial of preoperative radiation suggest that an interval > 2 weeks following the completion of radiation increases the chance of downstaging.[25] Most series recommend a 4- to 8-week interval.[26] Whether increasing the interval between the end of intensive short-course radiation and surgery to > 4 weeks will increase downstaging is not known. This question is being addressed in the ongoing Stockholm III trial.

Although preoperative chemoradiotherapy may adversely affect sphincter function, the impact is most likely less than that of postoperative chemoradiotherapy. Functional results continue to improve up to 1 year after surgery. Functional data from the German trial are pending.

Randomized Data
Bujko and colleagues performed a randomized trial of two preoperative approaches.[27] A total of 316 patients with cT3 rectal cancer were randomized to 5 Gy × 5 followed by surgery (at a median of 8 days) vs conventional preoperative chemoradiotherapy (50.4 Gy plus bolus fluorouracil [5-FU]/leucovorin daily × 5 at weeks 1 and 5) followed by surgery (at a median of 78 days). All tumors were above the anorectal sphincter, and TME was performed for distal tumors.

Compared with 5 Gy × 5, patients who received chemoradiotherapy had a significantly lower incidence of positive circumferential margins (4% vs 13%) but no significant difference in local failure (14% vs 9%) or 4-year survival (66% vs 67%). Furthermore, although a significantly higher pathologic complete response (pCR) rate (16% vs 1%) was noted, the incidence of sphincter preservation was not increased (58% vs 61%). It must be emphasized that the numbers of patients (316) were small for a randomized trial, surgeons were not encouraged to modify the operation based on the response to preoperative therapy, and no centralized radiation quality review was conducted. The German trial did have centralized quality control, and it was found that the treatment center, schedule, and gender were independent prognostic factors for local control.[28]

Results of similar randomized trials from Australia and Europe are pending. Similar to the German trial, patients underwent a pretreatment clinical assessment by the operating surgeon. In the subset of patients who were thought to require an abdominoperineal resection (APR), sphincter preservation was achieved in 21% of those who received chemoradiotherapy and 26% of those who received short-course radiation. The absence of a difference in sphincter preservation rate may have been related to a lack of the surgeon’s commitment to the concept of sphincter preservation. Since modification of the surgical approach following preoperative therapy is contrary to traditional oncologic teaching, sphincter-preserving surgery in a patient who would normally require an APR requires a surgeon who is comfortable with this change. The German trial controlled for this bias as the randomization was stratified by surgeon.

Positive Radial Margins
Although the distal margin is predictive of both local recurrence and the feasibility of a sphincter-preserving operation, the radial (circumferential) margin also has a substantial impact on the local recurrence rate. In the Dutch CKVO trial, 17% had positive circumferential margins. In a subset analysis by Nagtegaal et al, patients with positive radial margins who underwent TME alone had a local recurrence rate of 17% after a low anterior resection (LAR) and 30% after an APR.[29] Few centers, especially in the United States, perform the necessary pathologic examination to detect positive circumferential margins.[30] MRI can help identify patients who will have positive margins.[31-33] In a retrospective analysis reported by Bail et al, despite receiving preoperative combined-modality therapy, 504 patients with positive radial margins had a higher local recurrence rate (35% vs 11%) and lower 5-year survival (27% vs 73%) compared to those with negative radial margins.[34]

Postoperative treatment has limited ability to control positive radial margins. In the Medical Research Council (MRC) CR-07 trial, patients with positive radial margins who received postoperative chemoradiotherapy had an 11% local recurrence rate.[35] Likewise, in a subset analysis of the Dutch CKVO trial, 50 Gy postoperatively did not compensate for positive margins.[36]

Required Follow-up
In contrast with colon cancer, where 3-year disease-free survival is a primary endpoint, patients who receive postoperative adjuvant chemoradiotherapy for rectal cancer require follow-up beyond 5 years. In the INT 0114 postoperative chemoradiotherapy trial, local control and survival results continue to decrease after 5 years.[37] At 7 years, the local failure rate was 17% and the survival rate was 56% compared with 14% and 64%, respectively, at 5 years. Therefore, rectal adjuvant combined-modality trials require at least 7-year follow-up. Whether the same late local recurrences will be seen in patients undergoing preoperative chemoradiotherapy is unknown.

**Is Postoperative Adjuvant Chemotherapy Needed After Preoperative Chemoradiotherapy?**

Almost all randomized trials performed in the past 2 decades reveal a 10% to 15% survival benefit with 6 months of adjuvant 5-FU-based chemotherapy for patients with node-positive colon or rectal cancer. Two randomized trials have examined whether chemotherapy improves the results of preoperative radiation in patients with cT3 and/or node-positive rectal cancer. The European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial randomized 1,011 patients to receive preoperative 45 Gy with or without concurrent bolus 5-FU/leucovorin followed by surgery with or without four cycles of postoperative 5-FU/leucovorin.[38] Only 37% had a TME. The Fédération Francophone de la Cancérologie Digestive (FFCD) 9203 trial randomized 742 patients to preoperative 45 Gy with or without bolus 5-FU/leucovorin.[39] However, all patients were scheduled to receive postoperative chemotherapy, and this occurred in 73%.

The EORTC trial revealed a significant decrease in the local recurrence rate among patients who received preoperative chemoradiotherapy compared with radiation alone (8%-10% vs 17%, \( P < .001 \)), but postoperative adjuvant chemotherapy did not increase 5-year survival (65%). A subset analysis of the EORTC trial revealed that patients who responded to preoperative chemoradiotherapy did have a survival benefit from postoperative chemotherapy.[40] The FFCD trial reported a similar decrease in local recurrence (8% vs 17%, \( P < .05 \)), and a corresponding increase in the pCR rate (11% vs 4%, \( P < .05 \)). However, the investigators observed no survival benefit (68% vs 67%) with preoperative chemoradiotherapy compared with radiation alone.

In the EORTC trial, only 43% of patients received ≥ 95% of the planned dose of postoperative chemotherapy. The reason for this is not clear and may explain the negative results. We have noted a concerning trend in the US and some European centers not to encourage patients—especially those who have a pCR—to receive the remaining 4 months of postoperative adjuvant therapy. This unintended consequence of preoperative chemoradiotherapy is concerning because the benefit of adjuvant chemotherapy is based on a total of 6 months of chemotherapy. This trend may help explain the slow accrual to the US Intergroup E5204 trial (*Figure 1*). In order to address this issue, Chau and colleagues have examined the use of neoadjuvant CAPOX (capecitabine [Xeloda], oxaliplatin [Eloxatin]) followed by chemoradiotherapy. This approach circumvents the need for the 4 months of postoperative chemotherapy.[41] In their pilot trial of 77 patients, the pCR rate was 24%. Since there is a 6-month interval between diagnosis and surgery, the radiologic response rate was followed by MRI. After induction CAPOX, the overall response rate was 88%, which increased to 97% following the completion of chemoradiotherapy, suggesting that there was no detriment in response rates.
Based on these encouraging results, the Spanish GCR-3 randomized phase II trial compared this approach with conventional preoperative chemoradiotherapy followed by surgery and postoperative chemotherapy (Figure 2). An interim analysis of the first 48/108 patients revealed an increased pCR rate with the neoadjuvant CAPOX approach (19% vs 10%).

Although its utility is still being investigated in rectal cancer, in patients with node-positive colon cancer, the combination of continuous-infusion 5-FU, leucovorin, and oxaliplatin (FOLFOX) has
replaced bolus 5-FU/leucovorin as a standard postoperative chemotherapy treatment.[43] Therefore, for patients who receive preoperative chemoradiotherapy, four cycles of postoperative FOLFOX is recommended.

**Standard and Novel Combined-Modality Therapy Regimens**

The North Central Cancer Treatment Group (NCCTG) 85-47-51 postoperative chemoradiotherapy trial revealed a 10% survival benefit for patients who received 5-FU as a continuous infusion compared with bolus delivery. Therefore, when 5-FU is combined with radiation, either pre- or postoperatively, it should be delivered as a continuous infusion. Although this survival benefit with continuous-infusion 5-FU was not confirmed in the Intergroup 0144 trial, it was associated with a lower incidence of hematologic toxicity.[44]

Based on the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial, which reported equivalence with the Mayo regimen in patients with stage II and III colon cancer, it is reasonable to substitute capecitabine for 5-FU.[45] However, it must be emphasized that capecitabine has not been directly compared with continuous-infusion 5-FU, and this is one of the endpoints of the NSAPB R-04 rectal cancer trial (Figure 3). Although the NO1696 trial confirmed that in the first-line setting CAPOX is equivalent to FOLFOX in patients with metastatic colorectal cancer,[46] the results from a definitive trial addressing this question in the adjuvant setting (NSAPB C-07) are pending.

![Figure 3: NSAPB R-04 Trial—Protocol of randomized phase III trial. APR = abdominoperineal resection; CI = continuous infusion; 5-FU = fluorouracil; NSAPB = National Surgical Adjuvant Breast and Bowel Project; RT = radiation therapy; SP = sphincter-preserving surgery.](image)

The Cancer and Leukemia Group B (CALGB) 89803 colon trial illustrated that the survival benefit seen in the metastatic setting does not necessarily translate to the adjuvant setting.[47] Therefore, the use of CAPOX with concurrent radiation is still investigational. In contrast, based on the MOSAIC trial, which revealed a survival benefit with FOLFOX for node-positive colon cancer, FOLFOX plus concurrent radiation is acceptable, however, is not yet the standard of care. Both weekly or monthly FOLFOX regimens have been successfully used.[48,49] However, if the weekly regimen is used, the oxaliplatin dose, based on data from Ryan and associates, should be 50 mg/m² and not 60 mg/m².[50]

Chemotherapeutic agents such as capecitabine, oxaliplatin, and irinotecan (CPT-11) as well as targeted therapies such as bevacizumab (Avastin) and cetuximab (Erbitux), which have improved results in patients treated in the adjuvant and/or metastatic settings are currently incorporated into phase I/II combined-modality programs. Selected agents that have been studied in this setting include tegafur/uracil (UFT),[51] raltitrexed (Tomudex),[52] oxaliplatin,[48-50,53] irinotecan,[54,55] S-1,[55] gefitinib (Iressa),[56] bevacizumab,[57,58] cetuximab,[48] and capecitabine[59] with pelvic radiation therapy. Most studies suggest higher pCR rates with the addition of these agents compared with 5-FU alone. However, for some agents, this increased pCR rate is associated with an increase in
acute toxicity. Phase III trials are needed to determine if these regimens offer a local control or survival advantage compared with 5-FU- or capecitabine-based chemoradiotherapy regimens. The role of biologic agents such as bevacizumab is the subject of ongoing clinical trials. Preliminary phase I trials from Duke University[57] and M.D. Anderson Cancer Center[58] using preoperative chemoradiotherapy with CAPOX plus bevacizumab have revealed pCR rates of 18% to 24%, respectively.

Additional phase I/II trials examining the addition of cetuximab to preoperative combined-modality therapy had mixed results. Although the report from Heidelberg on CapeIri (capecitabine, irinotecan) reported a pCR rate of 25%,[60] other trials with 5-FU, capecitabine, or CAPOX have produced more limited rates of 5% to 12%.[48] Whether the benefit of patient selection based on wild vs mutated KRAS seen in patients with metastatic disease will be helpful in the adjuvant rectal setting is unknown.[58]

The Radiation Therapy Oncology Group (RTOG) 0012 randomized phase II trial enrolled 106 patients who received preoperative chemoradiotherapy with either continuous-infusion 5-FU plus twice-daily radiation or FOLFIRI (leucovorin, 5-FU, irinotecan) plus conventional daily fractionated radiation.[61] Although the pCR rate was 26% in both arms, the grade 3+ toxicity rates were 42% and 55%, respectively. Neither of these preoperative regimens were brought into phase III trials.

The RTOG 0247 randomized phase II trial compared preoperative chemoradiotherapy with CapeIri vs CAPOX in 101 patients with cT3-4 disease.[62] Although not significant, patients who received CAPOX had a higher pCR rate (21% vs 10%) with a similar incidence of hematologic (4% vs 8%) and nonhematologic toxicity (29% vs 24%).

**Impact of Tumor Response to Preoperative Chemoradiotherapy**
Although some series show no correlation,[63] most series suggest that outcome improves with increasing pathologic response to preoperative chemoradiotherapy.[64-66] Analysis of biopsies examining selected molecular markers[67,68] have had varying success in helping to select patients who may best respond to preoperative therapy. Since these studies are limited retrospective trials and most do not examine multiple markers, the need for adjuvant therapy should still be based solely on T and N stage. Fortunately, the new Intergroup rectal trials prospectively collect tissues for these and other markers.

In one series, the value of radical surgery in patients with a biopsy-proven complete response was questioned.[69] However, it included patients with cT1-3 disease and has not been reproduced by
other investigators. In series limited to patients with cT3 disease who have received preoperative chemoradiotherapy, radical surgery is still necessary to fully evaluate pathologic response. Neither posttreatment ultrasound[12] nor physical exam (which is only 25% accurate)[70] are sufficient. The use of FDG-PET[14,71,72] and diffusion MRI[73] as noninvasive measures of response are being investigated, and mixed results have been reported. Glynne-Jones and associates reviewed 218 phase II and 28 phase III trials of preoperative radiation or combined-modality therapy. They confirmed that clinical and/or radiologic response do not sufficiently correlate with pathologic response to recommend a “wait and see” approach to surgery following preoperative therapy.[74]

**Radiation Sensitizers, Protectors, and Novel Fractionation and Delivery Techniques**

Randomized trials have investigated the use of sucralfate enemas to decrease acute radiation proctitis, olsalazine (Dipentum) and mesalazine to decrease acute enteritis, and butyric acid to decrease chronic radiation proctitis.[75] The results of all these trials have been negative. The radioprotector WR-2721 did not reduce toxicity in early trials, but a more recent study suggests a benefit.[76] Rectally administered amifostine is well tolerated. However, its efficacy remains to be determined.[77]

Hyperfractionated radiation has been examined in phase I/II trials.[78] In general, the pCR rates may be improved but at the expense of increased acute toxicity. The incidence of acute grade 3+ toxicity in the RTOG R-0012 arm receiving 5-FU plus twice-daily radiation (1.2–45.6 Gy, with a boost of 9.6–14.4 Gy) was 42%. Hyperfractionated and accelerated fractionated radiation, especially in combination with chemotherapy, remains investigational.

The clinical utility of three-dimensional (3D) treatment planning is being investigated.[49,79] The most important contributions of 3D treatment planning include the ability to plan and localize the target and normal tissues at all levels of the treatment volume and to obtain dose-volume histogram data. An analysis of 3D treatment planning techniques at the Massachusetts General Hospital suggests that the volume of small bowel in the radiation field is decreased with protons as compared with photons.[80] Intensity-modulated radiation therapy (IMRT) treatment planning techniques can further decrease the volume of small bowel in the field.[81] However, the clinical benefit of IMRT compared to 3D or conventional treatment delivery remains to be determined.

This article is reviewed here: Thirty Years of Rectal Cancer Research: A Brief History & Treating Rectal Cancer: Key Issues Reconsidered

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