Current Status and Future Directions in Preoperative Chemoradiotherapy of Rectal Cancer

By Claus Rödel, MD

Overview: **With optimized local treatment for patients with locally advanced rectal cancer, achieved through preoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) and total mesorectal excision surgery, local recurrence rates are less than 10%. The development of distant metastasis is now the predominant mode of failure in rectal cancer (30% to 35%). Newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, irinotecan, and targeted therapies, such as bevacizumab and cetuximab, have been incorporated into phase I to III studies with preoperative radiotherapy (RT) for rectal cancer. Defining the best sequence of combinations, including induction chemotherapy before CRT, and the best sequence of targeted therapies are currently addressed in clinical trials. Future improvement in patient selection for tailoring treatment may result from biologic analysis of tumor sensitivity. The current monolithic approach to apply the same schedule of preoperative 5-FU-based CRT to all patients with tumor-node-metastasis system stage II/III rectal cancer must be questioned.**

CRT AND SURGICAL resection are important elements of multimodality treatment for patients with locally advanced rectal cancer. The optimum sequence of these modalities has been addressed in several randomized trials and preoperative CRT has been shown to be superior to postoperative treatment for a variety of endpoints. The National Surgical Adjuvant Breast and Bowel Project R-03 trial was closed prematurely because of poor patient accrual, but results were recently reported for 254 (of intended 900) patients after a median follow-up for surviving patients of 8.4 years. The 5-year disease-free survival was significantly improved for patients treated with preoperative compared with postoperative therapy (65% compared with 53%, p = 0.011); 5-year overall survival for patients treated preoperatively was 75% compared with 66% for patients treated postoperatively (p = 0.065).[1] The 5-year cumulative incidence of locoregional recurrence as a first event was 10.7% in each arm. A German study—Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the German Cancer Society (CAO/ARO/AIO)-94—was completed with more than 820 patients.[2] Compared with postoperative CRT, the preoperative combined modality approach was superior in terms of local control (6% compared with 13%, p = 0.006), acute toxic effects (27% compared with 40%, p = 0.001), and chronic toxic effects (14% compared with 24%, p = 0.012). Sphincter preservation in those patients judged by the surgeon to require an abdominoperineal resection was also improved with preoperative CRT (39% compared with 19%; p = 0.005).

Two further randomized trials have examined whether concomitant 5-FU-based chemotherapy improves the results of preoperative, conventionally fractionated RT in patients with T3/4 rectal cancer. The European Organisation for Research and Treatment of Cancer 22921 was a four-arm randomized trial of preoperative 45 Gy with or without concurrent bolus 5-FU/leucovorin followed by surgery with or without four cycles of postoperative 5-FU/leucovorin.[3] A significant decrease in local recurrence was observed in three chemotherapy groups: 8.8%, 9.6%, 8.0% with either preoperative CRT, postoperative chemotherapy, or both, respectively, compared with 17.1% without treatment (p = 0.002). The 5-year overall survival was not affected by chemotherapy at the median follow-up of 5.4 years: 65.6% compared with 64.8% (p = 0.79) for preoperative CRT compared with preoperative RT; 67% compared with 63% (p = 0.132) for postoperative chemotherapy compared with no postoperative chemotherapy.

The second trial—Foundation Française de Cancérologie Digestive 9203—compared preoperative 45 Gy with or without bolus 5-FU/leucovorin, and all patients received postoperative chemotherapy.[4] An improvement in the pathologic complete response (pCR) rate was observed (11.4% compared with 3.6%, p = 0.0001) and local recurrence was lower with preoperative CRT: 8.1% compared with 16.5% of preoperative RT (p = 0.004). Overall survival at 5 years was the same (67%). Given all these data from randomized trials, 5-FU-based preoperative CRT is now the preferred treatment for patients with locally advanced rectal cancer.

Integrating Multidrug Chemotherapy into Preoperative Combined Modality Treatment

With optimized local treatment, achieved through preoperative CRT and total mesorectal excision surgery, local recurrence rates are less than 10%. The development of distant metastasis is now the predominant mode of failure in rectal cancer (30% to 35%). Thus, integrating more effective systemic therapy into combined modality programs is the challenge. Newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, and irinotecan, are now being incorporated into phase I and II studies for rectal cancer as well.[5] Most of the phase I and II studies revealed higher pCR rates in the range of 15% to 30% compared with 5-FU alone (10% in the German trial). However, for some agents, with this increased pCR rate is an associated increase in acute toxicity. The Radiation Therapy Oncology Group (RTOG) reported two phase II randomized trials. RTOG-0012 enrolled 106 patients who received preoperative CRT with either 5-FU plus twice-daily radiation compared with 5-FU/leuvovorin and irinotecan plus conventional daily fractionated radiation.[6] Although the pCR rates were 26% in

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Table 1. Ongoing Phase III Trials with Novel Drugs for Patients with Rectal Cancer

	Preoperative Treatment	Surgery	Postoperative Treatment	Primary Endpoint	Study Status
ACCORD 12/0405	RT 45 Gy + CAP vs.	TME	Postoperative CT free in each institution	Histopathologic complete remission rate	Follow-up
	RT 50 Gy + CAP + OX	TME	Postoperative CT free in each institution		
STAR-01	RT 50.4 Gy + 5-FU vs.	TME	5-FU based CT	Disease-free survival	Follow-up
	RT 50.4 Gy + 5-FU + OX	TME	5-FU based CT		
NSABP-R-04	RT 50.4 Gy + 5-FU vs.	TME	Patients may enter ECOG-E5204	Loco-regional relapse rate	Recruiting
	RT 50.4 Gy + 5-FU + OX vs.	TME			Recruiting
	RT 50.4 Gy + CAP vs.	TME			Recruiting
	RT 50.4 Gy + CAP + OX	TME			Recruiting
ECOG-E5204	RT 40–55.8 Gy + Chemotherapy according to NSABP-04 or 5-FU PVI/CAPE ± OX or 5-FU + LV	TME	OX + 5-FU/LV vs. OX + 5-FU/LV+ BEV	Overall survival	Follow-up
		TME			
Chirurgische Arbeitsgemeinschaft für Onkologie/Arbeitsgemeinschaft Radiologische Onkologie/ Arbeitsgemeinschaft Internistische Onkologie (CAO/ARO/AIO)-04	RT 50.4 Gy + 5-FU vs.	TME	5-FU vs.	Disease-free survival	Recruiting
	RT 50.4 Gy + 5-FU + OX	TME	5-FU + OX		
PETACC-6	RT 45 Gy + CAP vs.	TME	CAP vs.	Disease-free survival	Recruiting
	RT 45 Gy + CAP + OX	TME	CAP + OX		

Abbreviations: ACCORD, Actions Concertées dans les Cancers Colorectaux et Digestifs; RT, radiotherapy; CAP, capecitabine; TME, total mesorectal excision; CT, chemotherapy; OX, oxaliplatin; STAR, Studio Nazionale Terapia neoAdiuvante Retto; FU, fluorouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; ECOG, Eastern Cooperative Oncology Group; PVI, protracted venous infusional; LV, leucovorin; BEV, bevacizumab; CAO, Chirurgische Arbeitsgemeinschaft für Onkologie; ARO, Arbeitsgemeinschaft Radiologische Onkologie; AIO, Arbeitsgemeinschaft Internistische Onkologie; PETACC, Pan-European Trials in Alimentary Tract Cancer.

both arms, the grade 3 or higher toxicity rates were 42% and 55%, respectively. Neither of these preoperative regimens were moved into phase III trials. In a more recent trial, the RTOG compared preoperative CRT with capecitabine plus irinotecan compared with capecitabine plus oxaliplatin in 101 patients with T3 or T4 disease (RTOG-0247). Although not statistically significant, patients who received capecitabine plus oxaliplatin had a higher pCR rate (21% compared with 10%) with similar hematologic (4% compared with 8%) and nonhematologic toxicity (29% compared with 24%).

Phase III trials are needed to determine if these regimens offer a local control or survival advantage compared with 5-FU or capecitabine CRT regimens. These studies have now been started in Europe and the United States (Table 1). Interestingly, early results from the Actions Concertées dans les Cancers Colorectaux et Digestifs (ACCORD) and Studio Nazionale Terapia neoAdiuvante Retto (STAR) trials did not confirm a significant improvement of early endpoints (such as the pCR rate) with the addition of oxaliplatin.[7,8] Long-term results are awaited.

KEY POINTS

- The current standard for the treatment of stage II and III rectal cancer is the use of continuous infusion 5-fluorouracil (5-FU) concomitantly with preoperative radiotherapy followed by total mesorectal excision and four cycles of adjuvant 5-FU.
- With this treatment, local recurrence rates are less than 10%. The development of distant metastasis is now the predominant mode of failure in rectal cancer (30% to 35%).
- Newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, irinotecan, and targeted therapies, such as bevacizumab and cetuximab, have been incorporated into phase I and II studies with preoperative radiotherapy for rectal cancer.
- These combinations must be investigated in larger phase III trials before they are endorsed in the routine neoadjuvant treatment of rectal cancer.
- Future developments will aim at identifying and selecting patients for the ideal treatment alternatives.

Role of Induction Chemotherapy Prior to Chemoradiotherapy

Traditionally, strategies used to deal with the problem of distant metastasis have often been to apply induction chemotherapy before CRT. Chau and et al[9] have examined the use of four cycles of induction capecitabine plus oxaliplation (CAPOX) followed by CRT with capecitabine. Their pilot trial of 77 patients reported a 24% pCR rate. Since there was a 6-month interval between diagnosis and surgery, the radiologic response rate was followed by magnetic resonance imaging. After induction chemotherapy, the overall response rate was 88%. The response rate increased to 97% following the completion of CRT, suggesting that there was no detriment in response rates. Based on these encouraging results, a Spanish randomized phase II trial was developed comparing this approach with conventional preoperative CRT followed by surgery and postoperative chemotherapy. A total of 108 patients received preoperative 50.4 Gy plus CAPOX and were randomly assigned to receive 4 months of CAPOX by induction or adjuvantly.[10] Although the pCR rates were not different (14% compared with 13%), both grade 3 or higher toxicity was lower (19% compared with 54%, $p = 0.0004$) and the ability to receive all four chemotherapy cycles was higher (92% compared with 57%, $p = 0.0001$) with the induction approach. This strategy, however, may also be associated with its own caveats, such as selection of radio-resistance clones, induction of accelerated repopulation, possibly reduced compliance to CRT, and substantial delay of definitive surgery.[11]

Integrating Molecular Targeted Agents into Preoperative Combined Modality Treatment

An emerging strategy to further improve outcome is to incorporate newer, biologically active, targeted therapies. Phase I and II trials of preoperative CRT have now been initiated to evaluate epidermal growth factor receptor (EGFR) inhibitors as radiosensitizers in rectal cancer. Machiels et al[12] have reported the safety and efficacy of combining preoperative RT with capecitabine and cetuximab in a phase I/II trial. This combination was associated with no unexpected toxicity; full doses of RT, chemotherapy, and cetuximab could be applied. However, only two (5%) of 37 patients achieved a pCR and a total of 25 (68%) of 37 patients had only moderate or minimal tumor regression. The German Rectal Cancer Study Group conducted a multicenter phase I/II study to determine the tolerability and efficacy of adding cetuximab to preoperative RT with capecitabine and oxaliplatin.[13] Again, only four (9%) of the 45 operated patients had pCR in the resected specimen, and 53% of patients had only moderate, minimal, or no tumor regression at all. As shown in Table 2, the disappointingly low pCR rates achieved by the combination of CRT plus cetuximab has now been confirmed in a variety of phase II studies.[14,15] Several mechanisms may contribute to the apparently subadditive interaction between CRT and cetuximab, including upregulation of cycline-dependent kinase p27 and G1 cell cycle arrest, the redundancy of EGFR pathways, K-ras mutation status, and sequence dependencies. However, it is also well conceivable that the benefit of such a combination may not be manifested as an increase in early tumor regression but rather as an arrest in tumor progression. Thus, longer follow-up (and finally randomized trials) is needed to draw any firm conclusions with respect to local and distant failure rates.

Preclinical data have suggested that proangiogenic factors, especially the vascular endothelial growth factor (VEGF), are upregulated in tumors in response to RT and may increase resistance to RT. These findings are now supported by clinical data in patients with rectal cancer, such that VEGF expression has been linked to a worse prognosis.[16] VEGF-targeted therapy may lead to a "normalization" of the tumor vasculature, thereby leading to greater tumor oxygenation and drug penetration. When combined with RT, antibodies against VEGF induced additive to supra-additive tumor growth delay and cell death in colon cancer models. Willett et al[17] have reported on a phase I study of preoperative bevacizumab, 5-FU, and radiation therapy for clinical T3 or T4 rectal cancer. Preliminary data indicate safety of this regimen and significant activity (six of seven evaluable patients demonstrated only microscopic disease in the surgical specimen 7 weeks after completion of neoadjuvant treatment). In a meticulous analysis of the first six patients performed 12 days after the first bevacizumab infusion, this group revealed a significant decrease in tumor blood perfusion and blood volume and a significant decrease in tumor microvessel density. This was accompanied by an increase in pericyte coverage of tumor vessels and a decrease of the interstitial fluid pressure, indicating that a "normalization" of the tumor vasculature by anti-VEGF treatment may contribute to the high efficacy of bevacizumab in this and further trials with combined CRT and VEGF inhibition (Table 3).[18-21] As a word of caution, the toxicity pattern (e.g., radiation-induced enteritis, perforations) and surgical complications (wound healing, fistula, bleeding) observed in at least some of the clinical studies warrants further investigations of the interaction of radiotherapy with VEGF inhibition, both for tumor and normal tissues.

Molecular Markers for Patient Selection

Tumor response of rectal cancer to preoperative therapy varies considerably. Histopathologic tumor regression ranges from a complete response with no viable tumor cells left to virtually no regression at all despite uniform treatment protocols, indicating a differential individual sensitivity of rectal cancer cells.[22] If one was able to identify patients with a responsive tumor at the time of diagnosis, a selective and individualized policy of preoperative therapy as well as less radical surgery might be pursued.

Table 2. Selected Phase II Studies of Preoperative Chemoradiotherapy for Rectal Cancer with EGFR Inhibition

Series	Number of Patients	Treatment	Toxicity	pCR
Rödel et al[13]	48	Preoperative RT: 1.8–50.4 Gy Capecitabine: 825 mg/m^2 bid d 1–14 and 22–35 Oxaliplatin: 50 mg/m^2 for d 1, 8, 22,29 Cetuximab: 400 mg/m^2 loading dose (d 7) followed by 250 mg/m^2 (d 1, 8, 15, 22, 29)	G 3–4 diarrhea: 19%	9
Horisberger[15]	50	Preoperative RT: 1.8–50.4 Gy Capecitabine: 500 mg/m^2 bid d 1–38 Irinotecan: 40 mg/m^2 for d 1, 8, 15, 22, 29 Cetuximab: 400 mg/m^2 loading dose (d 1) followed by 250 mg/m^2 (d 8, 15, 22, 29)	G 3–4 leukopenia: 4% G 3 diarrhea: 30%	8
Bertolini[14]	40	Preoperative RT: 2.0-50 Gy 5-FU: 225 mg/m^2 continuous infusion Cetuximab: 400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly, 3 times, followed weekly concomitantly with CRT	G 3 acneiform rash: 15%; no grade 4 toxicity	8
Debucquoy[24]	41	Preoperative RT: 1.8–45 Gy Capecitabine: 825 mg/m^2 during RT Cetuximab: 400 mg/m^2 loading dose (d 7) followed by 250 mg/m^2 (d 1, 8, 15, 22, 29)	G 3 diarrhea: 15% G 4: myocardial infarction (1), pulmonary embolism (1), sepsis (1)	5

Abbreviations: EGFR, epidermal growth factor receptor; pCR, pathologic complete response; RT, radiotherapy; bid, twice a day; d, day; G, grade; FU, fluorouracil; CRT, chemoradiotherapy.

Table 3. Selected Phase II Studies of Preoperative Chemoradiotherapy for Rectal Cancer with VEGF Inhibition

Series	Number of Patients	Treatment	Toxicity	pCR
Marijnen et al[20]	23	Preoperative RT: 2.0–50 Gy Capecitabine: 825 mg/m^2 bid Bevacizumab: 5 mg/m^2 on d −14, 1, 15, 29 Surgery 6–10 wks thereafter	G 3: skin (4), diarrhea (2); Grade 4: anal mucositis (1); G 5: enteritis with uncontrollable bleeding (1), Postoperative: 2/23 small bowel perforations, 1 rectal wall perforation, surgical: perineal dehiscence (1), rectovaginal fistula (2), bleeding 5,500 mL (1)	9
DiPetrillo et al[21]	23	Two biweekly courses of bevacizumab 5 mg/m^2 and modified FOLFOX6 followed by bevacizumab 5 mg/m^2 biweekly, oxaliplatin 50 mg/m^2 weekly (subsequently reduced to 40 mg/m^2 due to grade 3 diarrhea), 5-FU 200 mg/m^2 continuous infusion concurrent with 50.4 Gy pelvic irradiation	G 3 during CRT: 75%	25
		Surgery 4–8 wks after completion of RT	G 4: neutropenia (1), diarrhea (1)	
Willett et al[18]	32	Preoperative RT: 1.8–50.4 Gy 5-FU: 225 mg/m^2 continuous infusion Bevacizumab: 5 or 10 mg/m^2 on d −14, 1, 15, 29 Surgery: 7–9 weeks after completion of RT	No acute grade 4 G 3 diarrhea: 22% Postoperative complications: wound infection (3), delayed healing (2), presacral abscess (2), pelvic hematoma (2), ileus (2)	16 (ypT0)
Crane et al[19]	25	Preoperative RT: 1.8–50.4 Gy Capecitabine: 900 mg/m^2 bid Monday-Friday Bevacizumab: 5 mg/m^2 on d 1, 15, 29 Surgery 6–11 wks (median 7.3) after RT	No G 3 GI or hematologic toxicity Surgical: 3 wound complications that required surgical intervention	32

Abbreviations: VEGF, vascular endothelial growth factor; pCR, pathologic complete response; RT, radiotherapy; bid, twice a day; d, day; G, grade; FOLXFOX, 5-fluorouracil, folinic acid, oxaliplatin; FU, fluorouracil; CRT, chemoradiotherapy; GI, gastrointestinal.

Either by genome-wide or candidate gene approaches, several proteins have been described to be putatively involved in the response of rectal carcinoma to RT and CRT, including key factors of the apoptotic and cell-cycle pathways. In a recent extensive review on molecular biomarkers investigated for their ability to predict outcome in rectal patients with cancer, Kuremsky et al[23] identified 1,204 articles with 36 putative biomarkers in the literature. If restricted to patients treated with preoperative CRT and to gene products with more than five studies, only p53, EGFR, thymidylate synthase, Ki-67, p21, and bax/bcl-2 met these criteria. Of these, quantitatively evaluated EGFR or EGFR polymorphisms, thymidylate synthase polymorphisms, and p21 have been identified as promising candidates that should be evaluated in larger prospective trials for their ability to guide preoperative therapy.

The study of Machiels et al, mentioned above, included a translational part with biopsies taken at three time points, at baseline, after the loading dose of cetuximab but before start of CRT, and at surgery. Microarray gene expression analysis and proteomics revealed downregulation of invasion and proliferation pathways and an upregulation of inflammatory pathways and EGFR ligands after the first dose of cetuximab.[24] The immunohistochemically determined expression of Ki-67 and TGF-alpha correlated with T-level down-categorization. At least a trend ($p = 0.06$) for better tumor regression was found for patients with wild-type K-ras. Bengala et al[25] identified the gene copy number of EGFR as a significant predictor for better tumor regression in their study of cetuximab plus 5-FU-based preoperative RCT ($p = 0.0016$). Mutated K-ras was associated with reduced tumor regression, albeit not significantly ($p = 0.12$). In patients with wild-type K-ras, tumor regression grade of 3 to 4 was 58.8% compared with 7.7% in cases with high or low gene copy numbers of EGFR, respectively ($p = 0.0012$).

Candidate biomarkers for response to bevacizumab-based CRT include VEGF, placenta-derived growth factor, plasma VEGF receptor 1, interleukin 6, and circulating endothelial cells.[18] Gene expression profiles of cancer cells in tumor biopsies before and 12 days after treatment with bevacizumab in patients with rectal cancer revealed an upregulation of stromal cell-derived factor 1 alpha (SDF1-alpha), its receptor CXCR4, and CXCL6, and downregulation of PIGF, Ang1, and Ang2. Higher SDF1-alpha plasma levels during bevacizumab treatment significantly associated with distant metastasis at 3 years.[26]

Conclusion and Future Perspectives

Evidently, the monolithic approaches, established by studies more than a decade ago, to either apply the same schedule of preoperative 5-FU-based CRT to all patients with tumor-node-metastasis system stage II/III rectal cancer or to give preoperative intensive short-course RT according to the Swedish and Dutch concept for all patients with resectable rectal cancer, irrespective of tumor stage and location, must be questioned. The inclusion of different multimodal treatments into the surgical oncologic concept, adapted to the tumor location and stage and to an individual patient's risk factors, is mandatory. Clearly, future developments will aim at identifying and selecting patients for the ideal treatment alternatives. Thus, clinicopathologic and molecular features as well as accurate preoperative imaging will take an important and integrative part in multimodality treatment of rectal cancer.

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Author	Employment or Leadership Positions (Commercial Firms)	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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