Rectal cancer: state of the art in 2012

Claus Rödel[a], *Ralf Hofheinz*[b], *and Torsten Liersch*[c]

Purpose of review
To discuss the recent developments of multimodal treatment for patients with local advanced rectal cancer, including incorporation of new chemotherapeutic and targeted agents, and the optimal sequence and timing of treatment components.

Recent findings
Five randomized trials have been completed to determine whether the addition of oxaliplatin to preoperative, fluorouracil-based chemoradiotherapy (CRT) offers an advantage compared to single-agent fluorouracil CRT. Early results from the ACCORD 12, STAR-01, and NSAPB R-04 trials did not confirm a significant improvement of early efficacy endpoints with the addition of oxaliplatin, whereas the German CAO/ARO/AIO-04 did. Most of the phase II trials incorporating cetuximab into CRT reported disappointingly low rates of pathologic complete response (pCR); the combination of CRT with VEGF inhibition showed encouraging pCR rates; however, it was associated with increased surgical complications. Novel clinical trials address the role of induction chemotherapy, of delayed, minimal or omitted surgery following CRT, or the omission of radiotherapy for selected patients.

Summary
At this time, the use of oxaliplatin or targeted agents as component of multimodality treatment for rectal cancer outside of a clinical trial is not recommended. The inclusion of different treatment options, according to tumor stage, location, imaging features, and response, will render the multimodal treatment approach of rectal cancer more risk-adapted.

Keywords
combined modality treatment, novel trials, oxaliplatin, rectal cancer, targeted agents

INTRODUCTION

Radiotherapy, chemotherapy, and surgical resection are the important elements of multimodal treatment for patients with locally advanced rectal cancer. The optimum sequence and combination of these modalities have been addressed in several randomized trials, and preoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) has been shown to be the preferred treatment for a variety of endpoints, including treatment compliance, toxicity, downstaging, and local control. Following the publication of the German intergroup phase III trial (CAO/ARO/AIO-94) in 2004, preoperative radiotherapy with infusional 5-FU, total mesorectal excision (TME) surgery, and adjuvant chemotherapy with 5-FU for 4 months has become a standard of care for stage II and III rectal cancer in Germany, most parts of Europe and the USA [1].

With optimized local treatment, achieved by preoperative radiotherapy/CRT and TME surgery, local recurrence rates have been markedly reduced. Distant metastases are now the predominant mode of failure in rectal cancer. None of the recently published randomized trials on combined modality treatment for rectal cancer, using either preoperative short-course radiotherapy alone or preoperative radiotherapy combined with 5-FU, has demonstrated a survival benefit – which remains true even after a follow-up of more than 10 years now for the German CAO/ARO/AIO-94 trial and the Dutch TME trial [2,3▪▪]. Any improvement in overall survival rates will require better control of systemic disease while keeping the rate of local recurrences below 5–10%. This review will discuss the most recent developments of multimodal treatment for patients

[a]Department of Radiotherapy and Oncology, University of Frankfurt, Frankfurt, [b]Interdisciplinary Tumour Center Mannheim, University of Heidelberg, Heidelberg and [c]Department of General Surgery, University of Göttingen, Göttingen, Germany

Correspondence to Claus Rödel, MD, Department of Radiotherapy and Oncology, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany. Tel: +49 69 6301 5130; fax: +49 69 6301 5091; e-mail: claus.roedel@kgu.de

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KEY POINTS

- Current standard for the treatment of rectal cancer is either the use of preoperative short-course radiotherapy or preoperative, conventionally fractionated radiotherapy with continuous infusion 5-FU, total mesorectal excision surgery, and 4 months of adjuvant 5-FU chemotherapy.
- With this treatment, local recurrences have been markedly reduced; the development of distant metastases is now the predominant mode of failure.
- Newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, irinotecan, and targeted therapies, such as bevacizumab and cetuximab, have been incorporated into clinical trials; however, at this time, the use of oxaliplatin or targeted agents as component of the multimodality treatment outside of a clinical trial is not recommended.
- Novel clinical trials address the role of induction chemotherapy, of delayed, minimal or omitted surgery following chemoradiotherapy, or the omission of radiotherapy for selected patients.

with locally advanced rectal cancer, including incorporation of new chemotherapeutic and targeted agents, and the optimal sequence and timing of treatment components.

INTEGRATING COMBINATION CHEMOTHERAPY INTO THE COMBINED MODALITY PROGRAM

Newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, and irinotecan, have been incorporated by several groups within phase I–III trials of preoperative CRT. A recent randomized phase III trial in Germany confirmed noninferiority for the endpoint overall survival when infusional 5-FU was replaced by the oral prodrug capecitabine during radiotherapy and adjuvant chemotherapy [4]. Early phase II trials adding oxaliplatin or irinotecan to 5-FU/capecitabine-CRT suggested higher pathologic complete response (pCR) rates when compared historically with preoperative 5-FU-CRT alone [5]. However, for these agents, with this increased pCR rate was an associated increase in acute toxicity. A total of five randomized phase III trials have subsequently been started and meanwhile completed in Europe and the USA to determine whether these combination chemotherapy CRT regimens offer an advantage compared with 5-FU-based combined modality regimen (Table 1). Early results from the ACCORD12/0405-Prodige 2 trial, STAR-01, and NSAPB R-04 trial did not confirm a significant improvement of early endpoints (such as the pCR rate) with the addition of oxaliplatin [6,7▪▪,8]. The most recent phase III trial of the German Rectal Cancer Study Group (CAO/ARO/

Table 1. Phase III trials adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy in stage II and III rectal cancer

Trial	Preoperative treatment	Surgery	Postoperative treatment	First results/comment
ACCORD 12 [6]	RT 45 Gy + capecitabine versus	TME	Postoperative CT free in each institution	pCR: 14 versus 19% (n.s.)
	RT 50 Gy + capecitabine + oxaliplatin	TME	Postoperative CT free in each institution	Grade 3/4 toxicity increased
STAR-01 [7▪▪]	RT 50.4 Gy + 5-FU PVI versus	TME	5-FU-based CT	pCR: 16% both arms
	RT 50.4 Gy + 5-FU + oxaliplatin	TME	5-FU-based CT	Grade 3/4 toxicity increased
NSABP R-04 [8]	RT 50.4 Gy + 5-FU versus	TME	No specific recommendations	pCR: 19 versus 21% (n.s.) Grade 3/4 toxicity increased
	RT 50.4 Gy + 5-FU + oxaliplatin versus	TME		
	RT 50.4 Gy + capecitabine versus	TME		
	RT 50.4 Gy + capecitabine + oxaliplatin	TME		
CAO/ARO/ AIO-04 [9]	RT 50.4 Gy + 5-FU versus	TME	5-FU versus	pCR 13 versus 17% ($P=0.04$) Grade 3/4 toxicity not increased
	RT 50.4 Gy + 5-FU + oxaliplatin	TME	5-FU + oxaliplatin	
PETACC 6	RT 45 Gy + capecitabine versus	TME	Capecitabine versus	Accrual completed
	RT 45 Gy + capecitabine + oxaliplatin	TME	Capecitabine + oxaliplatin	

ACCORD, Actions Concertées dans les Cancers Colorectaux et Digestifs; CAO/ARO/AIO, Chirurgische Arbeitsgemeinschaft für Onkologie/Arbeitsgemeinschaft Radiologische Onkologie/Arbeitsgemeinschaft Internistische Onkologie; CT, chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, pathological complete remission; PETACC, Pan-European Trials in Alimentary Tract Cancer; PVI, protracted venous infusion; RT, radiotherapy; STAR, Studio nazionaleTerapia neoAdiuvante Retto; TME, total mesorectal excision.

AIO-04) has successfully completed accrual in 2010 with more than 1250 patients recruited. This trial randomized patients either to the best arm of the former CAO/ARO/AIO-94 trial, that is, 5-FU-based preoperative CRT, surgery, and four cycles of postoperative 5-FU chemotherapy, or to the investigational arm that incorporated oxaliplatin both into preoperative CRT as well as postoperative adjuvant chemotherapy. First results were presented at ASCO 2011 and indicate that the addition of oxaliplatin to 5-FU-based CRT, with the doses and intensities as used in this trial (a chemotherapy gap was introduced in week 3 of radiotherapy), was well tolerated, associated with high compliance rates and increased pCR rates compared to 5-FU-CRT alone [9]. The primary endpoint of CAO/ARO/AIO-04 is disease-free survival at 3 years. Thus, longer follow-up is needed to assess the impact of adding oxaliplatin to fluorouracil-based CRT on long-term efficacy endpoints.

INDUCTION AND ADJUVANT COMBINATION CHEMOTHERAPY

Given the fact that the cumulative doses of the new drugs reached during preoperative CRT are substantially lower than in adjuvant colon cancer trials and probably not able to sufficiently reduce distant metastases, the question that needs to be addressed is how and when to apply systemic treatment with adequate dose and intensity. A randomized trial (CHRONICLE) investigated the postoperative chemotherapy with capecitabine and oxaliplatin (CAPOX) versus observation only after preoperative 5-FU-based CRT; however, this trial has unfortunately been closed because of poor accrual.

Recently, a Spanish randomized phase II trial was developed comparing the induction chemotherapy approach with conventional preoperative CRT followed by surgery and postoperative chemotherapy [10▪]. A total of 108 patients received preoperative 50.4 Gy plus CAPOX and were randomized to receive 4 months of CAPOX either by induction or adjuvant. Notably, all 54 patients who commenced induction chemotherapy also received CRT and underwent surgery. Although the pCR rates, downstaging and tumor regression grading were similar, both grade at least 3 toxicity was lower (19 versus 54%, $P = 0.0004$) and the ability to receive all four chemotherapy cycles was higher (92 versus 57%, $P = 0.0001$) with the induction approach. With a median follow-up time of 39 months, the 3-year DFS rates were 68% for the induction chemotherapy arm and 70% in the adjuvant chemotherapy arm ($P = 0.97$). Whether or not the improvement in applicability and dose-density of chemotherapy will ultimately translate into improved disease-free survival will have to be tested in a larger phase III trial.

INTEGRATING TARGETED AGENTS INTO THE COMBINED MODALITY PROGRAM

The epidermal growth factor receptor (EGFR) is a promising target of antitumor treatment because it participates in cell division, inhibition of apoptosis, and angiogenesis. Preclinical investigations have linked EGFR expression with radioresistance both *in vitro* and *in vivo*. Clinical phase I/II studies of preoperative CRT have subsequently been performed to evaluate EGFR inhibitors as radiosensitizers in rectal cancer (Table 2) [11▪]. Intriguingly, almost all of these trials reported disappointingly low rates of pathological complete remission (pCR) following the combination of CRT plus cetuximab [12–18]. If compared to similar regimens with CRT alone, the pCR rates did not seem to be higher when cetuximab was added to CRT [19]. Thus, it has been speculated that the concurrent administration of EGFR inhibitors may interfere with the antitumor activity of CRT, for example, through the strong antiproliferative property that may compromise the effect of CRT to target proliferating tumor cells. Several correlative studies attempted to elicit

Table 2. Selected phase II studies of preoperative chemoradiotherapy for rectal cancer with EGFR inhibition

Series	*n*	Neoadjuvant treatment	G3–G4 toxicity	pCR
Valentini *et al.*, 2008 [12]	33	RT 50.4 Gy + 5-FU + gefitinib	Gastrointestinal 20.5%	30%
Rödel *et al.*, 2008 [13]	48	RT 50.4 Gy + capecitabine/oxaliplatin + cetuximab	Diarrhea 19%	9%
Horisberger *et al.*, 2009 [14]	50	RT 50.4 Gy + capecitabine/irinotecan + cetuximab	Leukopenia 4%, diarrhea 30%	8%
Bertolini *et al.*, 2009 [15]	40	RT 50 Gy + 5-FU + cetuximab	Acneiform rash 15%	8%
Debucquoy *et al.*, 2009 [16]	41	RT 45 Gy + capecitabine + cetuximab	Diarrhea 15%	5%
Kim *et al.*, 2011 [17]	40	RT 50.4 Gy + capecitabine/irinotecan + cetuximab	Leukopenia 10%, diarrhea 5%	23%
Pinto *et al.*, 2011 [18]	60	RT 50.4 Gy + 5-FU/oxaliplatin + panitumumab	Diarrhea 39%, skin 19%, nausea 5%	21%

RT, radiotherapy.

molecularly defined subgroups that may benefit from the addition of cetuximab. However, thus far, no single marker or pattern of markers, including EGFR, KRAS, BRAF, PTEN, etc., could be unambiguously identified to have predictive or prognostic value [16,20,21].

One common feature of all the clinical trials reported so far is that the primary endpoint chosen to assess the efficacy of CRT with EGFR inhibitors was the early surrogate endpoint pCR. It is well conceivable, however, 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 or reduction in tumor relapse. The EXPERT-C trial is a randomized phase II trial that investigated the addition of cetuximab to induction chemotherapy with CAPOX, preoperative CRT, TME, and postoperative CAPOX in 164 patients with MRI-defined high-risk rectal cancer (Fig. 1). The pCR rates with or without cetuximab were 11 versus 7% ($P = 0.71$), and the 3-year progression-free survival was 80 versus 81% ($P = 0.67$) [22]. Noteworthy, recurrences occurred later during follow-up with the addition of cetuximab, and the 3-year overall survival was improved (96 versus 91%, $P = 0.035$). Potential future strategies with EGFR inhibitors and CRT in rectal cancer include the combination with irinotecan rather than oxaliplatin, the use of anti-EGFR agents as induction/consolidation therapy rather than concomitant with CRT, the combination with other molecular targets, and better selection based on molecular predictors [11▪].

Angiogenesis is necessary for the survival and growth of tumors; however, tumor blood vessels are often characterized by a disorganized architecture that contributes to intratumoral regions of intermittent or chronic hypoxia. Preclinical data have suggested that proangiogenic factors, especially the vascular endothelial growth factor (VEGF), are upregulated in tumors in response to radiotherapy and may increase the resistance to radiotherapy. These findings are now supported by the clinical data in rectal cancer patients, such that VEGF expression has been linked to a worse prognosis [23]. VEGF-targeted therapy may lead to a 'normalization' of the tumor vasculature, thereby leading to greater tumor oxygenation and drug penetration.

Willett *et al.* [24] were the first to report on a phase I study of preoperative bevacizumab, 5-FU, and radiotherapy 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 trial.

Meanwhile, several phase II studies with combined CRT and VEGF inhibition have been performed and showed encouraging pCR rates (Table 3) [25–32]. However, caution is recommended

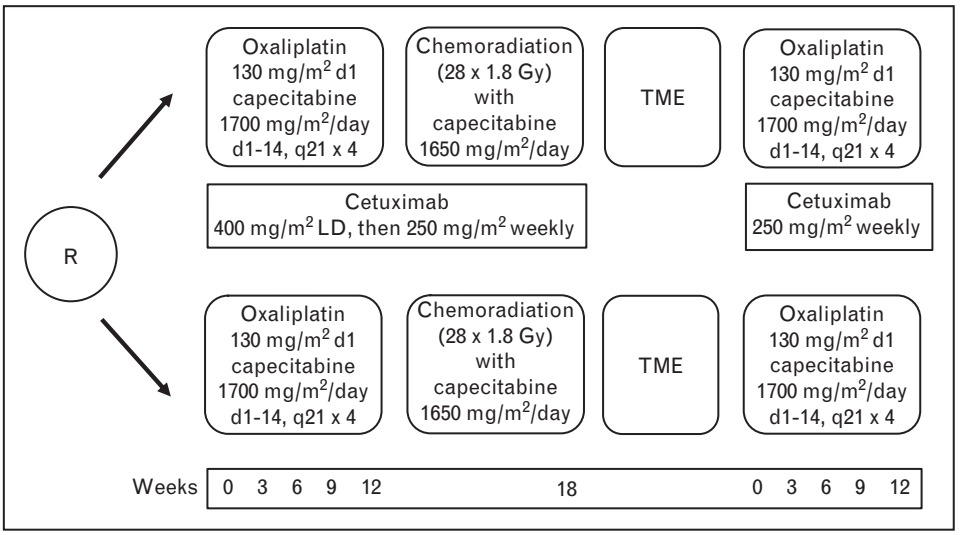

FIGURE 1. EXPERT-C Trial: Randomized phase II trial of induction chemotherapy with capecitabine/oxaliplatin, preoperative chemoradiotherapy, surgery, and adjuvant chemotherapy with or without cetuximab in MRI-defined high-risk patients. LD, loading dose; TME, total mesorectal excision.

Table 3. Selected phase II studies of preoperative chemoradiotherapy for rectal cancer with VEGF inhibition

Series	*n*	Neoadjuvant treatment	G3–G4 toxicity/surgical morbidity	pCR
Willett *et al.*, 2009 [25]	32	RT 50.4 Gy + 5-FU + bevacizumab	Diarrhea 22%/wound infection (3), delayed healing (2), presacral abscess (2), pelvic hematoma (2), ileus	16% (ypT0)
Crane *et al.*, 2009 [26]	25	RT 50.4 Gy + capecitabine + bevacizumab	No grade 3 GI or hematologic toxicity/ wound complications that required surgical intervention (3)	32%
Velenik *et al.*, 2011 [27]	61	RT 50.4 Gy + capecitabine + bevacizumab	Dermatitis 10%, proteinuria 6.5%, leukopenia 5%	13%
Spigel *et al.*, 2011 [28]	35	RT 50.4 Gy + 5-FU + bevacizumab	Diarrhea 14%, neutropenia 14%/ bowel perforation (1), pelvic infection (1)	29%
Kennecke *et al.*, 2011 [29]	42	RT 50.4 Gy + capecitabine/oxaliplatin + bevacizumab	Diarrhea 24%, pain 10%/postoperative infection 13%, re-operation because of complications 11%	18%
Resch *et al.*, 2011 [30]	8	RT 45 Gy + capecitabine + bevacizumab	Intestinal bleeding 25%, diarrhea 25%, perianal, abdominal pain 25%. Accrual terminated because of grade 3 toxicities	25%
Nogue *et al.*, 2011 [31]	47	Bevacizumab + capecitabine/oxaliplatin (4 cycles) + RT 50.4 Gy + capecitabine + bevacizumab	Diarrhea 11%, neutropenia 6%/surgical re-intervention because of complications 24%	36%
Dipetrillo *et al.*, 2012 [32]	26	Bevacizumab + 5-FU/folinic acid/ oxaliplatin (1 month) + RT 50.4 Gy + 5-FU/oxaliplatin + bevacizumab	Grade 3/4 overall 76%/postoperative complications 36%. Accrual terminated early because of toxicity	20%

RT, radiotherapy.

regarding the toxicity pattern (radiation-induced enteritis and perforations) and surgical complications (wound healing, fistula, and bleeding) observed in at least some of the clinical studies. At this time, the use of targeted agents as component of the multimodality treatment for rectal cancer outside of a clinical trial is not recommended.

NOVEL CLINICAL TRIAL DESIGN: DELAYED, MINIMAL, OR OMITTED SURGERY

The most commonly used time interval between completion of preoperative CRT and surgical resection has traditionally been 4–6 weeks. An emerging body of data suggests that – reminiscent to anal cancer treatment – the response to CRT in patients with rectal cancer is time-dependent, and maximal local tumor regression may well take longer than the standard 6 weeks to surgery. Several retrospective series have addressed the time interval as predictor of tumor response, surgical morbidity, and long-term outcome. In a series of 132 patients with locally advanced rectal cancer, Tulchinsky *et al.* [33] found that patients operated on more than 7 weeks after CRT had similar rates of perioperative complications as compared to patients operated on less than 7 weeks after CRT; however, the longer CRT-to-surgery interval was associated with significantly improved pCR rates (35 versus 17%, $P = 0.03$) and significantly better disease-free survival. These results were supported by Kalady *et al.* [34] who found a 31% pCR rate in patients receiving surgery more than 8 weeks after CRT compared to 16% in patients operated on within 8 weeks of CRT.

As these retrospective studies suggested an improved response with an interval longer than 6 weeks after completion of CRT, with no tumor progression during this period and no negative impact on surgical operability after the longer interval, several groups used this prolonged interval between CRT and surgery for adding chemotherapy. The Timing of Rectal Cancer Response to Chemoradiation Consortium in the United States conducted several sequential prospective phase II trials of preoperative CRT (50.4–54 Gy with 225 mg/m^2/day continuous infusion 5-FU during radiotherapy) and delayed the time point of surgery. Study group 1 underwent surgery 6 weeks after completion of CRT ($n = 66$). Patients in study group 2 ($n = 70$) received two additional cycles of chemotherapy (modified FOLFOX6) during the waiting period before surgery (total time between completion of CRT and surgery: 11–13 weeks). The pCR rate of 70 patients treated in study group 2

was 25% compared with 18% for study group 1 without an apparent increase in surgical complications [35▪]. Investigators from the UK are currently evaluating an interval of 8–12 weeks versus standard 4–6 weeks between completion of CRT and surgery (NCT01037049).

The American College of Surgeons Oncology group has recently completed the Z6041 phase II trial of patients with clinical T2N0 rectal cancer who received preoperative CRT (total dose 54 Gy) with capecitabine and oxaliplatin followed by transanal local excision 6 weeks after completion of CRT. Among 77 patients who underwent local excision, 34 patients had a pCR (44%), 49 (64%) had ypT0–1, and 4 (5%) ypT3 tumors. All but one had negative margins. Grade of at least 3 acute toxicity during CRT occurred in 39% of patients, and rectal pain was the most common postoperative complication [36]. Clearly, longer follow-up is needed to assess the long-term oncologic outcome.

Maas *et al.* [37▪▪] reported on a wait-and-see policy for patients with clinical complete response (cCR) after neoadjuvant CRT (50.4 Gy, concurrent capecitabine). If re-staging, performed 6–8 weeks after completion of CRT by use of clinical examination, high-resolution MRI, and endoscopy plus biopsies, indicated no residual tumor or residual fibrosis only, patients were eligible for a nonoperative approach combined with intensive follow-up. In this series, 21 of the 192 patients treated initially (11%) had evidence of cCR and were included for a wait-and-see policy. With a median follow-up of 25 months, only one patient developed a local recurrence (successfully treated with salvage surgery), 20 patients are alive without disease. These patients with cCR included in a wait-and-see policy did at least as well as a control group of 20 patients with a pCR after radical surgery, but had less toxicity and better short-term bowel function. Thus, this study is in line with the earlier results reported by Habr-Gama *et al.* [38]. Although we need substantially more follow-up and larger numbers of patients to validate this approach, these results raise the possibility of a nonoperative approach for selected patients with locally advanced rectal cancer.

NOVEL CLINICAL TRIAL DESIGN: OMITTED RADIOTHERAPY

Given the acute and long-term side-effects of radiotherapy, other novel approaches address whether radiotherapy can be omitted in selected patients. In a single-institution series of patients with mid-lying and high-lying rectal cancer (T4 tumors excluded), Schrag *et al.* [39] used six cycles of preoperative fluorouracil, folinic acid, and oxaliplatin plus bevacizumab (cycles 1–4 only) without the addition of radiotherapy in 30 patients. All patients had a R0 resection and 25% had a pCR. The U.S. Alliance cooperative group plans to validate this approach in a multicenter, randomized clinical trial for selected patients (tumor >5 cm from anal verge and >3 mm from mesorectal resection margin).

CONCLUSION

Evidently, the monolithic approaches to either apply the same schedule of preoperative 5-FU-based CRT to all patients with TNM stage II/III rectal cancer or to give preoperative short-course radiotherapy to all patients irrespective of tumor stage and location, need to be questioned. The inclusion of different multimodal treatment concepts, adapted to tumor stage, location, molecular profiles, response, and to the patient's risk factors and preferences is upcoming [40▪]. Future developments will aim at identifying and selecting patients for their most appropriate treatment alternatives. These may include omission of radical surgery (e.g., for early, low-lying, CRT-responsive tumors that would otherwise require an abdominoperineal resection) and omission of radiotherapy (e.g., for mid-/high lying tumors without threatened circumferential resection margins). Further, treatment algorithms that need to be validated include induction chemotherapy protocols with or without (biomarker-driven) targeted agents and CRT (e.g., for patients with high-risk criteria, such as T4, N2, and extramural venous invasion). Thus, clinicopathological and molecular features as well as accurate imaging will take an integrative part in the multimodality treatment of rectal cancer.

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Conflicts of interest

C. Rödel has received honoraria from Roche, Sanofi-Aventis, and is currently receiving a research grant from Merck. R. Hofheinz is currently receiving research grants from Roche, Amgen, and Merck, and indicated board memberships and consultancy for Roche and Merck. T. Liersch declared no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 459).

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This phase III trial showed increased toxicity, reduced compliance, and no improvement of pCR rates when weekly oxaliplatin was added to 5-FU-based chemoradiotherapy. The primary endpoint, overall survival, needs longer follow-up. Importantly, this study did include oxaliplatin only into preoperative chemoradiotherapy, not adjuvant chemotherapy. It remains to be seen whether the cumulative doses applied will have an impact on overall survival.

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