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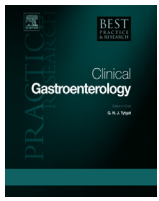

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Rectal cancer: Neoadjuvant chemoradiotherapy

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A B S T R A C T

The monolithic approach to apply the same schedule of preoperative 5-fluorouracil (5-FU)- or capecitabine-based chemoradiotherapy (CRT) to all patients with clinically staged TNM stage II/III rectal cancer need to be questioned. Five randomized trials have been completed to determine if the addition of oxaliplatin to preoperative 5-FU/capecitabine-based CRT offers an advantage compared with single-agent CRT. In contrast to the German CAO/ARO/AIO-04 trial, results from the ACCORD 12, STAR-01, PETACC-6 and NSAPB R-04 trials failed to demonstrate a significant improvement of early or late efficacy endpoints with the addition of oxaliplatin. Most of the phase II trials incorporating cetuximab into CRT reported disappointingly low rates of pCR; the combination of CRT with VEGF inhibition showed encouraging pCR rates but at the cost of increased surgical complications. Novel clinical trials currently address (1) the role of induction and consolidation chemotherapy before or after CRT, (2) minimal or omitted surgery following complete response to CRT, or (3) the omission of radiotherapy for selected patients with response to neoadjuvant chemotherapy. The notion of different multimodal treatment concepts according to tumor stage, location, mesorectal fascia margin status, molecular profiles, tumor response, and patients' preferences becomes increasingly popular and will render the multimodal treatment approach of rectal cancer more risk-adapted.

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Radiotherapy (RT), chemotherapy, and surgical resection are important elements of the multimodal treatment for patients with locally advanced rectal cancer. The optimum sequence and combination of these modalities has 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, acute and chronic toxicity, downstaging, sphincter preservation, and local control [1–4]. Following the publication of the German phase III trial (CAO/ARO/AIO-94) in 2004, preoperative RT with infusional 5-FU, total mesorectal excision (TME) surgery, and adjuvant chemotherapy with 5-FU for four months has become a standard of care for stage II and III rectal cancer in Germany, most parts of Europe and the United States [1].

With optimized local treatment, achieved by preoperative RT/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 RT alone or preoperative RT combined with 5-FU, has demonstrated a survival benefit – which remains true even after a follow-up of more than ten years now for the German CAO/ARO/AIO-94 trial and the Dutch TME trial [5,6]. Hence, any improvement in disease-free and 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 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 non-inferiority for the primary endpoint overall survival when infusional 5-FU was replaced by the oral prodrug capecitabine during RT and adjuvant chemotherapy [7]. Early phase I–II trials adding oxaliplatin or irinotecan to neoadjuvant 5-FU/capecitabine-CRT suggested higher pathologic complete response (pCR) rates when compared historically with preoperative 5-FU-CRT alone [for review: [8]]. However, for these agents, increased pCR rate was associated with increased acute toxicity.

Subsequently, five randomized phase III trials were conducted in Europe and the United States to determine if these combination chemotherapy CRT regimens offer an advantage compared with 5-FU-based combined modality treatment (Table 1). Results from the phase III STAR-01, ACCORD 12, NSABP-R04 and PETACC-6 trials did not confirm a significant improvement of early endpoints, such as the pCR rate, with the addition of oxaliplatin to preoperative 5-FU-based CRT [9–16]. Acute toxicity was significantly increased and compliance to preoperative radiotherapy and concurrent chemotherapy reduced with the addition of oxaliplatin to 5-FU/Capecitabine-based CRT. Also, long-term endpoints, including local relapse rates, disease-free (DFS) and overall survival, were not significantly different with or without the addition of oxaliplatin (Table 1).

The most recent phase III trial of the German Rectal Cancer Study Group (CAO/ARO/AIO-04) 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, i.e. 5-FU-based preoperative CRT, surgery, and four cycles of postoperative bolus 5-FU chemotherapy, or to the investigational arm that incorporated oxaliplatin both into preoperative CRT as well as postoperative adjuvant chemotherapy. The 5-FU dosage and schedule were different in the control and investigational arms, which may have contributed to the different outcomes. First results showed that the addition of oxaliplatin to 5-FU-based CRT, with the doses and intensities used in this trial (note that a chemotherapy gap was introduced in week three of RT, based on previous phase I/II studies), was well-tolerated, associated with high compliance rates and increased pCR rates compared to 5-FU-CRT alone [14]. The primary endpoint of CAO/ARO/AIO-04 was DFS. With a median follow-up of 50 months, this primary endpoint was significantly improved in the oxaliplatin-containing treatment arm (three-year DFS 71.2% versus 75.9%, HR 0.79, 95% CI 0.64–0.98, $p = 0.03$) [15]. Given the discrepant results between the German CAO/ARO/