The best timing for administering systemic chemotherapy in patients with locally advanced rectal cancer

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Abstract: Over the past several decades, outcomes for patients with rectal cancer have improved considerably. However, several questions have emerged as survival times have lengthened and quality of life has improved for these patients. Currently patients with locally advanced rectal cancer (LARC) are often recommended multimodality therapy with fluoropyrimidine-based chemotherapy (CT) and radiation followed by total mesorectal excision (TME), with consideration given to FOLFOX before chemoradiotherapy (CRT). Recently, Garcia-Aguilar and colleagues reported in *Lancet Oncology* that the addition of mFOLFOX6 administered between CRT and surgery affected the number of patients achieving pathologic complete response (pathCR), which is of great interest from the standpoint of pursuit of optimal timing of systemic CT delivery. This was a multicenter phase II study consisting of 4 sequential treatment groups of patients with LARC, and they reported that patients given higher number CT cycles between CRT and surgery achieved higher rates of pathCR than those given standard treatment. There was no association between response improvement and tumor progression, increased technical difficulty, or surgical complications. Ongoing phase III clinical trial further assessing this strategy might result in a paradigm shift.

Keywords: Locally advanced rectal cancer (LARC); mFOLFOX6; neoadjuvant therapy

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Multimodality therapy consisting of concurrent fluoropyrimidine-based chemoradiotherapy (CRT), followed by surgery and systemic chemotherapy (CT), is the standard of care for patients with locally advanced rectal cancer (LARC); this is based on results of the German Rectal Cancer Study Group phase III trial (protocol CAO/ARO/AIO-94) (1). Although treatment outcomes and quality of life for patients with LARC have impressively improved over the past several decades, many controversies remain regarding the optimal treatment paradigm for this common disease—an estimated 39,610 new cases of rectal cancer occurred in the United States in 2014 (2).

Garcia-Aguilar and colleagues recently published a report (3) in which they assessed the impact of adding mFOLFOX6 between CRT and surgery on the proportion of patients achieving pathologic complete response (pathCR). This nonrandomized study consisted of 4 sequential study groups of patients with stage II-III LARC at centers in the United States and Canada; a total of 259 patients were analyzed (the 4 groups consisted of 60, 67, 67, and 65 patients). The primary endpoint was the proportion of patients who achieved pathCR in each study group, analyzed by intention to treat. Patients in group 1 were treated with CRT and underwent total mesorectal excision (TME) 6–8 weeks after CRT; the proportion achieving pathCR in this group was set as a baseline. Patients in groups 2–4 received 2, 4, or 6 cycles of mFOLFOX6 4–5 weeks after the completion of CRT and underwent TME 3–5 weeks after the last cycle of mFOLFOX6. CRT consisted of 225 mg/m^2 fluorouracil per day by continuous infusion throughout radiotherapy, which consisted of 45.0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5.4 Gy and possible second boost of 3.6 Gy, within which the entire small bowel

could be excluded from the final cone down (54 Gy total cumulative dose). Each cycle of mFOLFOX6 consisted of 200 or 400 mg/m^2 racemic leucovorin, according to the discretion of the treating investigator, as well as 85 mg/m^2 oxaliplatin in a 2-h infusion, bolus 400 mg/m^2 fluorouracil on day 1, and a 46-h infusion of 2,400 mg/m^2 fluorouracil. Disease response had been assessed using the Response Evaluation Criteria in Solid Tumors guidelines (4) during the neoadjuvant treatment course for patients in groups 2–4, so that they would not be at risk of disease progression due to the lengthened CRT-to-surgery interval.

They reported that an increased proportion of patients achieved pathCR with the addition of mFOLFOX6 between CRT and TME, and the lengthened CRT-to-surgery interval. The proportions of patients achieving pathCR were as follows: 11/60 in group 1 [18%; 95% confidence interval (CI), 10–30], 17/67 in group 2 (25%; 95% CI, 16–37), 20/67 in group 3 (30%; 95% CI, 19–42), and 25/65 in group 4 (38%; 95% CI, 27–51; P=0.0036). Patients in group 4 were significantly more likely to achieve pathCR than those in group 1 (odds ratio 3.49; 95% CI, 1.39–8.75; P=0.011). On the basis of these findings, the authors concluded that the additional mFOLFOX6 between CRT and surgery and prolongation of the CRT-to-surgery interval contributed to the increase in the proportion of patients achieving pathCR, which was among the highest proportions reported for LARC to date (5-9). The study also demonstrated that the treatment approach used in groups 2–4 did not increase the risk of tumor progression or surgical complications, which is favorable from both an oncologic and surgical standpoint.

However, this study has a number of limitations. First, because it was a nonrandomized phase II trial with a relatively small number of patients enrolled, unrecognized confounders and selection bias could have affected the results. Second, the primary endpoint was the proportion of patients achieving pathCR, which means limited follow-up, although pathCR is associated with high recurrence-free survival rates (5,10). Third, the trial was not originally powered to assess surgical and oncologic complications and the measurement of surgical complications was limited because only a few parameters were represented. Given these limitations, the findings of the study should be interpreted with caution and are still in need of confirmation in a randomized trial.

Current therapy for LARC, with a combination of CRT, TME, and systemic CT, has greatly improved patient outcomes, but many controversies remain even just within the neoadjuvant treatment setting. First, the optimal timing of the delivery of chemoradiation needs to be investigated further. The German Rectal Cancer Study Group compared preoperative CRT with postoperative CRT for LARC (1) and found that preoperative CRT resulted in improved local control and reduced toxicity, with similar overall survival outcomes to those observed with postoperative CRT. Including that study, several trials have been conducted to compare the administration of radiation preoperatively and postoperatively, but a clear answer has not yet been reached.

In terms of preoperative CRT, several options exist. Both preoperative short-course radiotherapy (5 Gy per day; total dose of 25 Gy) and preoperative CRT have been shown to improve local disease control in patients with LARC treated with surgery (11,12). Short-course radiotherapy followed by surgery within 7 days has the advantage of shorter treatment duration, more efficient use of medical resources, and fewer costs than CRT followed by surgery within 6–8 weeks. Unfortunately, two prospective randomized studies comparing short-course radiotherapy with CRT (13,14) did not provide a clear answer as to which is the most efficacious method.

In addition, several recent trials have shown that the oral capecitabine (converted to fluorouracil by intracellular thymidine phosphorylase) could be substituted for continuous venous infusion of fluorouracil, which would be easier for patients. In both a European trial (15) and the National Surgical Adjuvant Breast and Bowel Project R04 (16), capecitabine was not inferior to continuous venous infusion of fluorouracil, although long-term oncologic outcomes are still awaited.

Recent studies have also investigated whether oxaliplatin could be added to fluoropyrimidine as a radiosensitizer to improve treatment outcomes. Most of these trials failed to show improved clinical outcomes with oxaliplatin, and it was shown to result in more toxic effects and worse therapeutic ratios (7,8,16). Although the CAO/ARO/AIO-04 trial (9) showed an increased proportion of pathCR with similar toxic effects in patients treated with oxaliplatin and fluoropyrimidine compared with fluoropyrimidine alone, this finding must be interpreted with caution because the fluorouracil dosage and schedule were not same between the two arms. In summary, so far it is not recommended to add oxaliplatin to fluorouracil as a radiosensitizer during CRT for patients with LARC.

Targeted therapy with anti-vascular endothelial growth factor and anti-endothelial growth factor receptor agents is expected to enhance treatment strategies for

LARC, and plenty of targeted agents play a crucial role in the treatment of unresectable or metastatic colorectal cancer. The AVACROSS study assessed the efficacy and toxicity of bevacizumab added to induction CT followed by preoperative bevacizumab-based CRT in patients with LARC (17). Although that study demonstrated an impressive proportion of patients achieving pathCR with the addition of bevacizumab (36%, which is similar to the 38% achieving pathCR in group 4 of the study by Garcia-Aguilar and colleagues), with manageable toxic effects, 24% of patients experienced serious surgical complications that required additional surgical intervention. Several other phase II trials that assessed the effectiveness and feasibility of adding bevacizumab to the combined-modality treatment failed to reach the primary endpoint or demonstrated increased toxic effects or surgical complications, and thus did not proceed to phase III trials (18,19).

Other targeted therapies have also been studied. The randomized phase II EXPERT-C trial assessed neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by TME, and results of that study showed that the secondary endpoints of radiologic response and overall survival significantly improved in patients with wild-type KRAS/BRAF rectal cancer whose treatment included cetuximab. However, the primary endpoint of improved pathCR was not met (20). The SAKK41/07 trial, a randomized, multicenter, phase II trial, assessed the impact of adding panitumumab to neoadjuvant CRT in patients with wild-type KRAS LARC. In that study, the primary endpoint was pathologic near-complete response plus complete tumor response, which was achieved in 53% of patients in the panitumumab arm compared with 32% in the control arm. However, patients receiving panitumumab also experienced increased rates of grade 3 or higher toxic effects (21). On the basis of these findings, unfortunately, targeted therapies have so far failed to play a role in neoadjuvant treatment of patients with potentially resectable LARC outside of clinical trials.

Controversies surrounding the optimal LARC treatment strategy also extend to the multimodality treatment paradigm itself, although it is clear that coordination of preoperative treatment, surgery, and adjuvant therapy is important. The strategy of induction CT preceding CRT and surgery was added to the 2015 version of the National Comprehensive Cancer Network (NCCN) clinical practice guidelines as an acceptable option for the treatment of LARC, indicating that the strategy of shifting systemic therapy to earlier in the treatment is receiving a lot of attention. This may be in part because the advances in modern treatment for LARC, consisting of preoperative CRT and improved surgical techniques, have considerably decreased local disease recurrence rates, which are currently below distant recurrence rates. However, although preoperative CRT and TME have improved local disease control, overall survival and the incidence of distant metastasis with LARC remain problematic.

Despite the NCCN guideline recommendation for adjuvant systemic CT, up to 27% of eligible patients with LARC never start adjuvant CT and less than 50% (22) receive the full prescribed course without interruptions or delays, owing to postoperative complications, delayed recovery, or interference caused by the need for a temporary ostomy closure (23). Systemic CT has advanced as oxaliplatin was added to 5-fluorouracil and FOLFOX was later administrated, which has led to relatively high routine response rates of up to 50% for patients with metastatic colorectal cancer (24). The next key step to advance the treatment of LARC is to determine the optimal timing for delivery of systemic CT.

Several potential advantages of systemic CT given in earlier setting of multimodality treatment are early prevention or eradication of micrometastases, increased rates of pathCR, minimized time needed for a diverting ostomy, avoidance of the challenges of undergoing CT in the presence of an ostomy, and improved tolerance and completion rates of CT. Several studies have investigated the efficacy and feasibility of systemic CT in the neoadjuvant setting. Cercek and colleagues assessed the safety and efficacy of initial FOLFOX followed by CRT and TME in 61 patients with LARC (25). In that study, a relatively high proportion of patients (36%) achieved pathCR or clinical complete response without any serious adverse events causing treatment delay during administration of FOLFOX or CRT. The AVACROSS study, which we mentioned earlier, then assessed the impact of induction CT as well (17). Although patients in that study experienced serious surgical complications, which might have been caused mainly by the addition of bevacizumab, the high proportion of patients achieving pathCR (36%) is still impressive in terms of the efficacy of neoadjuvant CT.

The positive attention given to the strategy of administering systemic CT ahead of CRT and surgery leads to another question: why not administer systemic CT between CRT and surgery? Several studies have demonstrated an association between increased intervals from completion of CRT to surgery and an increase

in pathCR rates (26,27), which also suggests that this question is worth pursuing. The study by Garcia-Aguilar and colleagues (3) might serve as a first step to answer this question, but further research is needed to determine whether the results of the study will ultimately change clinical practice. The results of ongoing phase III trials assessing this strategy are awaited, although the question remains which factor, the length of the interval from CRT to surgery or the administration of mFOLFOX6, had the most effect on achieving increased the pathCR rates. Approaching the answers of those questions with further studies and improving the pathCR rate can also contribute to advance the discussion about wait-and-see nonoperative strategy, i.e., deferral of surgery and close follow-up in LARC patients with clinical complete response after CT and CRT, which is still part of clinical trial (28). For now, many controversies remain in terms of how to manage patients with LARC, but further studies of rigorous protocol-based treatment will help the management of rectal cancer become truly individualized. In addition, molecular assessment will need to be incorporated in personalizing care.

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Footnote

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