



How to Achieve a Higher Pathologic Complete Response in Patients With Locally Advanced Rectal Cancer Who Receive Preoperative Chemoradiation Therapy

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The current standard of care for treating patients with locally advanced rectal cancer includes preoperative chemoradiation therapy (PCRT) followed by a total mesorectal excision and postoperative adjuvant chemotherapy. A subset of these patients has achieved a pathologic complete response (pCR) and they have shown improved disease-free and overall survival compared to non-pCR patients. Thus, many efforts have been made to achieve a higher pCR through PCRT. In this review, results from various ongoing and recently completed clinical trials that are being or have been conducted with an aim to improve tumor response by modifying therapy will be discussed.

Keywords: Rectal cancer; Preoperative chemoradiation therapy; Pathologic complete response; Disease-free survival; Overall survival

INTRODUCTION

Colorectal cancer (CRC) is a major health concern in Korea. Nationwide cancer statistics in Korea report that more than 26,000 new cases of CRC were diagnosed in 2015 [1]. The current standard of care for patients with locally advanced rectal cancer (LARC) includes preoperative chemoradiation therapy (PCRT) followed by a total mesorectal excision (TME) and postoperative adjuvant chemotherapy [2]. Although this multimodal treatment strategy has achieved a significant reduction in the local recurrence rate after surgery, it has not achieved an improved survival of patients [3-9]. Interestingly, a subset of patients who achieved pathologic complete response (pCR) after PCRT showed improved disease-free survival (DFS) and overall survival (OS) com-

pared with non-pCR patients [10-13]. Moreover, the subgroup of patients who achieved a clinical complete response (cCR) after PCRT was able to do so with nonoperative management or a deferral of surgery strategy [14].

Furthermore, the treatment of patients with rectal cancer compromises their quality of life profoundly, mainly because of stoma formation. However, even after patients have received sphincter-saving procedures, such as a low anterior or an intersphincteric resection, they suffer from low anterior resection (LAR) syndrome, which occurs in up to 40% of patients after surgery [15].

This review will discuss recent clinical trials or approaches to improve tumor response by using various modifications of treatment. Because organ preservation strategies and watch-and-wait approaches are recent strategies, solid evidence supporting their survival benefits is lacking. Therefore, research on such treatments was not included in this review.

HOW TO ACHIEVE A HIGHER pCR AFTER PCRT IN LARC

Adding various cytotoxic or molecular target agents with radiation therapy to improve tumor response; less is more
Traditionally, 5-fluorouracil (5-FU) has been used as a radio-sensitizing agent in a neoadjuvant setting for the treatment of patients with rectal cancer. After a new cytotoxic agent, oxaliplatin, showed

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improved disease control in an adjuvant setting, many trials were conducted to improve the tumor response by adding more cytotoxic agents, or even molecular target agents, during radiation therapy. The results of recent clinical trials are summarized in Table 1. A German trial was the only one that showed statistically significant differences in the pCR rate by adding oxaliplatin to radiation therapy [16]. Other trials, including NSABP R-04, showed an increase in grade 3–4 chemotherapy-related toxicities and a decreased compliance of treatment when oxaliplatin was added [17–26]. Additionally, the NSABP R-04 trial showed that continuous infusion of 5-FU was equivalent to oral capecitabine in terms of pCR rate and downstaging of the tumor [17, 25]. Based on these clinical trials, many other recent trials have adopted oral capecitabine as a radiosensitizer.

Effect of increasing the time interval between completion of PCRT and surgery on the pCR rate

The decision to prolong the time interval from 2 weeks to 6 to 8 weeks to achieve a higher pCR is based on the findings of recent clinical trials [27]. More recently, some investigators have tried to delay surgery beyond the classical 6 to 8 weeks from the time of completion of radiation therapy. Petrelli et al. [28] performed a meta-analysis regarding prolonging the time interval and concluded that the pCR rate increased from 13.7% to 19.5% in the longer interval group (>6–8 weeks). However, OS, DFS, R0 resection rate, sphincter preservation and complication rates were similar between the longer interval (>6–8 weeks) and the shorter interval (<6–8 weeks) groups.

Recent studies have suggested an even longer waiting period of up to 12 weeks or more. A UK 6- vs. 12-week trial reported a pCR rate of 6% in the 6-week group compared with 20% in the 12-week group [29]. Conversely, the French GRECCA-6 study reported no differences in pCR rate between the 7-week and the 11-week groups, but postoperative complications (32% vs. 44.5%) were increased and the quality of TME specimens (90% vs. 78.7%) was poor in the 11-week group [30].

An increased waiting period might achieve pCR even in short-course radiation therapy [31]. However, concerns about tumor-cell repopulation during the prolonged waiting period have been expressed, so currently no consensus as to the length of the waiting period exists. Greater, well-designed randomized studies are needed to confirm the efficacy of an increased waiting period in the treatment of patients with rectal cancer.

Upfront or induction chemotherapy, followed by preoperative radiation therapy and/or adding consolidation chemotherapy during the waiting period, has led to the era of total neoadjuvant chemotherapy

Although PCRT has shown an improvement in local control, it has not shown improved DFS or OS for patients with LARC (Table 2) [3–9]. Upfront chemotherapies, such as induction or consolidation chemotherapy and total neoadjuvant therapy (TNT), have been introduced to improve and achieve survival benefits and are being actively tested in ongoing trials.

Updated National Comprehensive Cancer Network (NCCN) guidelines suggest induction chemotherapy with FOLFOX or CAPEOX followed by PCRT and transabdominal surgery as treatment options for patients with LARC [2]. Even though induction chemotherapy is not yet approved for coverage by Korean insurance, it has been widely applied in the care of patients with LARC. Gao et al. [32] reported the results of a phase-2 trial using neoadjuvant sandwich treatment with CAPEOX administered prior to and concurrently with flowing radiation therapy for patients with LARC. Among 49 eligible patients, 45 patients underwent optimal surgery, and the pCR rate was 42.2%. When the 4 patients with cCR who refused surgery were considered, the pCR rate rose to 46.9%. The French GRECCA-4 trial tested induction chemotherapy with FOLFIRINOX (5-FU, irinotecan and oxaliplatin) chemotherapy in patients with LAR [33]. Of these patients, 15% showed more than 75% tumor shrinkage 2 weeks after induction chemotherapy. The study was terminated early due to the relatively low treatment efficacy of induction chemotherapy; however, when the

Table 1. Summary of trials that added cytotoxic or molecular target agents to improve tumor response in radiation therapy for the treatment of patients with locally advanced rectal cancer

Trial	No. of patients	Chemotherapy regimen	PCR	P-value
STAR-01 [18]	705	5-FU PVI vs. 5-FU+oxaliplatin	16% vs. 16%	NS
ACCORD 12 [22, 23]	584	Capecitabine vs. CAPEOX	13.9% vs. 19.2%	0.09
NSABP R-04 [17, 25]	1,608	5-FU vs. 5-FU+oxaliplatin vs. capecitabine vs. CAPEOX	12.1% vs. 11.2%	0.70
CAO/ARO/AIO-04 [26]	1,236	5-FU vs. 5-FU+oxaliplatin	13% vs. 17%	0.04
PETACC-6	1,094	capecitabine vs. CAPEOX	12% vs. 14%	NS
Dellas et al. [19]	70	CAPEOX+bevacizumab	17.4%	-
EXPERT-C [21]	165	CAPEOX vs. CAPEOX+ cetuximab	7% vs. 11%	0.714
FOWARC TRIAL [20]	495	5-FU vs. mFOLFOX vs. no chemotherapy	14% vs. 27.5% vs. 6.6%	0.005

PCR, pathologic complete response; 5-FU, 5-fluorouracil; PVI, protracted venous infusion; NS, not significant; CAPEOX, capecitabine+oxaliplatin; mFOLFOX, modified 5-fluorouracil+oxaliplatin.

inclusion criteria of the patients, such as more than mrT3c or mrT4 tumors or a threatened circumferential resection margin less than 1 mm, were examined, induction chemotherapy might have played some role in the management of patients with LARC.

The main ideas of consolidation chemotherapy are in regard to the potential benefits of improved local and systemic control of LARC when chemotherapy is added during the waiting period between completion of PCRT and surgery. A timing trial reported both short- and long-term outcomes [34, 35]. That study divided patients into 4 groups according to the duration of consolidation chemotherapy. Compared with the no-consolidation group (pCR rate of 18%), adding 2-, 4-, and 6-cycles of FOLFOX consolidation chemotherapy resulted in pCR rates of 25%, 30%, and 38%, respectively. With a median follow-up of 59 months, DFS differed significantly between the no-consolidation group and the consolidation groups. Furthermore, the consolidation groups showed a better compliance to chemotherapy compared to the nonconsolidation group. Other studies, done by Polish and Korean groups used short-course radiation therapy for the treatment of patients with LARC and demonstrated an increased pCR rate with consolidation chemotherapy; however, the improved pCR rate was not statistically significant [31, 36].

Currently, the NCCN guidelines recommend 4 months of adjuvant fluoropyrimidine-based chemotherapy for all patients who

receive PCRT and undergo surgical resection, regardless of pathologic findings [2]. These recommendations are not based on direct evidence from randomized trials, but are instead supported by extrapolation from the demonstrated survival benefits in colon cancer adjuvant chemotherapy trials. To date, only 4 randomized clinical trials [37-40] and 1 meta-analysis [41] to test the benefits of adjuvant chemotherapy in the treatment of patients with rectal cancer have been published. Many compounding factors have precluded the finding of evidence in those trials. Of these factors, postoperative complications and resultant poor compliances in adjuvant chemotherapy should be considered. Adopting upfront systemic chemotherapy, which is a growing area of active research on treating patients with LARC, may be a way to overcome these limitations in the effective administration of adjuvant chemotherapy. Recent trials to evaluate the effectiveness of TNT are summarized in Table 3 [42-47]. Many potential benefits, such as early control of micrometastases and improved compliance of chemotherapy, can be achieved by delivering all scheduled systemic chemotherapy before surgery. Moreover, TNT that is effectively delivered before surgery may improve tumor response and increase the probability of successful sphincter-preserving surgery.

High-dose chemoradiotherapy

The traditional radiation dose for patients with LARC is 5,040

Table 2. Preoperative chemoradiation therapy for the treatment of patients with advanced rectal cancer did not show any survival benefit in most clinical trials

Trial	No. of patients	Study regimen	5-Year OS	P-value
Krook et al. [3]	204	Postop RT vs. Postop CCRT	49% vs. 58%	NS
Swedish rectal cancer trial [4]	908	Surgery alone vs. Preop SCRT	55% vs. 63%	0.008
Dutch trial [40]	1,861	TME alone vs. Preop SCRT	63% vs. 64%	NS
LYON R96-02 [5]	88	Preop RT vs. Preop RT+XBR	67% vs. 67%	NS
CAO/ARO/AIO [16]	823	Postop LCRT vs. Preop LCRT	74% vs. 76%	NS
FFCD 9203 [7]	762	Preop LCRT vs. Preop LCRT	67% vs. 67%	NS
MRC CR07 [9]	1,350	Preop SCRT vs. Postop LCRT	70% vs. 68%	NS

OS, overall survival; Postop, postoperative; Preop, preoperative; RT, radiotherapy; CCRT, chemoradiotherapy; NS, not significant; SCRT, short-course radiotherapy; TME, total mesorectal excision; XBR, external beam radiation; LCRT, long-course radiotherapy.

Table 3. Total neoadjuvant therapy (TNT) for the treatment of patients with locally advanced rectal cancer

Trial	No. of patients	Study regimen	PCR
GCR-3 [43]	108	Preop CAPEOX+CAPEOX CRT vs. CAPEOX CRT+adjuvant CAPEOX	14% vs. 13%
CONTRE [47]	39	FOLFOX+Cap CRT	33%
Marechal et al. [45]	57	FOLFOX+5-FU CRT vs. 5-FU CRT	32% vs. 34%
Schou et al. [46]	85	CAPEOX+Cap CRT	23%
AVACROSS [44]	47	Bev+XELOX followed by Bev+Cap CRT	36%
EXPERT [42]	105	CAPEOX+Cap CRT+Cap	20%

PCR, pathologic complete response; Preop, preoperative; CAPEOX, capecitabine+oxaliplatin; CRT, chemoradiotherapy; FOLFOX, 5-fluorouracil+leucovorin+oxaliplatin; Cap, capecitabine; 5-FU, 5-fluorouracil; Bev, bevacizumab; XELOX, capecitabine+oxaliplatin.

cGy or 2,500 cGy. A recent trial conducted in Denmark proposed increasing the radiation dose to 70 Gy, and this achieved a cCR in 78.4% of the patients [48]. Brachytherapy is also an alternative treatment option for patients that are medically unfit for surgical approaches [49, 50].

CONCLUSIONS

Despite recent advances in the treatment of patients with LARC, the OS of those patients has not significantly improved. PCRT remains the major treatment strategy to combat LARC, and reports that a subgroup of patients achieved a pCR after PCRT have greatly encouraged clinical and biological research that aims to identify the factors influencing pCR. However, no solid evidence for the benefit of a pCR after PCRT has yet to be reported, and no specific factors influencing pCR have yet to be identified. Many factors need to be considered if the OS of patients with LARC is to be improved. More information is needed in several areas, such as how to predict tumor response after PCRT, maximizing tumor response, determining the best time to assess tumor response, how to identify true cCR, etc.

Treatment paradigms for patients with LARC are slowly shifting from the current, standard trimodal treatment of PCRT followed by surgery and adjuvant chemotherapy to more aggressive perioperative treatments, such as induction or consolidation chemotherapy and total neoadjuvant therapy. This modification of treatment paradigms aims to improve local control, improve survival of patients, increase the frequency of sphincter-saving surgery, and possibly lead to an avoidance of surgery or to organ-preserving treatment for patients with rectal cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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