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REVIEW ARTICLE

# A review of preoperative chemoradiotherapy for lower rectal cancer

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**Abstract:**

In Western countries, rectal cancer has been treated by chemoradiotherapy (CRT) for several decades now, and good local control has been reported. However, Japanese guidelines did not strongly recommend CRT, because CRT is only useful for achieving local control and imbues no survival benefit. For this reason, CRT was rarely used to treat rectal cancer in Japan. However, in the 2000s, several studies involving CRT began to be reported from Western countries, such as "correlation between pathological complete response and survival," "induction chemotherapy followed by CRT," and "watch-and-wait policies." These studies were directly correlated with survival of and benefits to the patients. Given these findings, Japanese institutions have recently begun to introduce CRT for rectal cancer. Therefore, in the present study, we reviewed several topics regarding CRT for rectal cancer.

**Keywords:**

rectal cancer, chemoradiotherapy, radiosensitizer, adjuvant chemotherapy, lateral lymph node dissection

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## Introduction

In 2014, 48,000 patients were expected to die from colorectal cancer, including 33,000 from colon cancer and 15,000 from rectal cancer, making colorectal cancer the second-most common cause of cancer-related death in Japan[1)]. In women, colorectal cancer is the most common cause and in men, it is the third-most common cause of cancer-related death[1)]. Regarding the oncologic outcomes of colorectal cancer, there was no marked difference in outcomes between colon and rectal cancer at stages 0-II[2)]. However, at stage III, rectal cancer is associated with an approximately 10% higher risk of recurrence than colon cancer. One of the reasons for this is the higher incidence of local recurrence in rectal cancer than in colon cancer[2)]. Therefore, local control of locally advanced rectal cancer is important to reduce the rate of recurrence.

Regarding the available treatment strategies for rectal cancer, Heald developed total mesorectal excision (TME) in 1982; this is now the standard technique used for rectal cancer worldwide[3)]. While surgeons in Japan also adopted TME, Japanese guidelines recommended autonomic nerve-preserving lateral lymphadenectomy without chemoradiotherapy (CRT)[4)]. In contrast, Western countries made different histories and CRT without lateral lymphadenectomy came to be adopted as the standard approach in the treatment of locally advanced rectal cancer[4-13)]. In addition, after the establishment of the standard irradiation method, surgeons and radiologists in Western countries focused on improving the pathological complete response (pCR) rate using different radiosensitizers and/or dose escalation regimens, and recent intensive regimens have demonstrated pCR rates of 20%-30%[14,15)]. Consequently, pCR patients do not necessarily need to undergo surgical resection[16-20)]. On the other hand, in Japan, the significance of lateral lymphadenectomy has been studied, and recent reports have demonstrated the usefulness of lateral lymphadenectomy even with CRT for rectal cancer patients with lateral lymph node swelling[21,22)].

On the other hand, the development of new treatment strategies or revision of strategies for lower rectal cancer has recently been discussed. For example, early T3 rectal cancer does not require CRT, and the same prognosis can be ex-

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pected with primary surgery. In addition, short-course radiotherapy was not adopted in the United States due to the lack of a downstaging effect; however, a clinical trial showed that even with the short-course regimen, a longer waiting period until surgery did indeed induce downstaging[23].

Here, we summarize the current topics of rectal cancer treatment involving CRT.

### *1. Pathological assessments following CRT*

The aim of preoperative CRT for rectal cancer is to improve the local control and sphincter preservation; however, the tumor regression grade (TRG) of the primary tumor is associated with the oncologic outcomes and those reports demonstrated that favorable outcomes can be expected in patients who achieved pCR or near-pCR[24-29]. The reason for this may be the radiosensitivity of the primary tumor that reflects the biological malignancy, including the probability of distant metastasis. Several studies have explained the biological mechanisms underlying this principle[30-32]. For example, the presence of a survivin inhibitor (an apoptosis protein) was associated with a significantly higher risk of recurrence and radioresistance in rectal cancer patients after CRT than the lack of this protein[30]. Furthermore, survivin is an important metastasis gene, and chemoresistance in colorectal cancer patients may be associated with its increased expression[31,32]. The radiosensitivity of the primary tumor is therefore closely linked to the frequency of distant metastasis, and TRG may be useful for evaluating the oncologic outcomes *in vivo* for rectal cancer. Given these previous findings, surgeons and radiologists have attempted to improve the TRG score by either increasing the radiation dose or achieving the concomitant use of an additional chemosensitizer with 5-FU-based chemotherapy.

*1a. High dose of chemoradiotherapy*

For the treatment of rectal cancer, a radiation dose of 45-50.4 Gy is recommended for locally advanced rectal cancer in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) consensus guideline. However, Burbach found that dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR rates and acceptable early toxicity[33]. In addition, Appelt demonstrated a significant dose-response relationship for tumor regression after preoperative CRT for locally advanced rectal cancer for dose levels in the range of 50.4-70 Gy[34]. These findings suggest that over 50 Gy of radiotherapy may be clinically relevant with acceptable toxicity; however, no major prospective trials exploring doses over 50 Gy have been performed yet, and the delivery of over 45 Gy of irradiation for small intestinal cancer significantly increased the rate of adverse effects. Further studies are therefore needed to confirm the safety and efficacy of dose escalation. Recently, irradiation techniques have been improved by using multiple-field irradiation and intensity-modulated radiotherapy[35,36]. These techniques have the potential to increase the radiation dose without compromising the safety.

*1b. Using additional drugs with 5-FU-based chemosensitizers*

In the NCCN and ESMO consensus guideline, 5-FU-based chemosensitizers are recommended with conventional RT for the treatment of locally advanced rectal cancer. Several studies have investigated the usefulness of additional drugs with 5-FU-based chemosensitizers to improve the response rate. We herein review the outcomes of those studies.

*a) Oxaliplatin (Table 1)*

Five prospective phase III randomized studies have focused on the effects of oxaliplatin with 5-FU-based chemotherapy: ACCORD, STAR-01, CAO/ARO-04, NSABP R04, and FOWARC trials[10,15,37-39]. Three of these five trials (STAR-01, CAO/ARO-04, and NSABP R04) noted no increase in the pCR rate, whereas the other two trials (ACCORD and FOWARC) noted an increase in the pCR rate. However, four of the five trials noted a significant increase in the rate of Grade 3 and 4 adverse events, especially leukopenia, diarrhea, and radiation dermatitis. Three of the five negative trials concluded that oxaliplatin should not be used as a radiosensitizer, whereas the other two recommended its use. One reason underlying the negative outcomes of adding oxaliplatin may be poor treatment compliance. In general, treatment compliance was defined as having completed at least 80% of the protocol-prescribed therapy. However, in the trials with negative outcomes, such as NSABP R04, the oxaliplatin compliance rate was only about 60%; in contrast, the compliance rate in the two trials with positive outcomes was over 80%. CAO/ARO-04 also recommended the use of oxaliplatin as adjuvant chemotherapy. Therefore, patients who can receive the full dose of oxaliplatin during the perioperative treatment period can expect favorable outcomes.

The tolerance toward 5-FU and oxaliplatin differs by performance status, age, characteristics, and race, among other parameters. The relatively good tolerance observed in the German trial of CAO/ARO/AIO-04 prompted the authors to conclude that the addition of oxaliplatin can be deemed as a new treatment option for locally advanced rectal cancer patients. However, the poor tolerance observed in the US trial of NSABP R04 prompted the authors to recommend against adding oxaliplatin.

In Japan, there are no recommended radiosensitizers, although some institutions have used S-1. The outcomes of the trials in foreign countries could not be directly applied to the Japanese population because the tolerance toward chemotherapy drugs differs between Japanese and Western populations. In 2015, a multicenter phase II study of preoperative CRT with S-1 (80 mg/m$^2$) plus oxaliplatin (80 mg/m$^2$) for locally advanced rectal cancer (SHOGUN trial) found that preoperative CRT with S-1 plus oxaliplatin resulted in a high pCR rate (27.4%) with a favorable toxicity profile[40]. However, evidence regarding the usefulness of adding oxaliplatin as a radiosensitizer for treating rectal cancer is still lacking.

*b) CPT-11 (Table 2)*

So far, no phase III trials have assessed the usefulness of

**Table 1.** Phase III Trials Adding Oxaliplatin to Preoperative Chemoradiotherapy in Rectal Cancer

| | Time country | Regimen | Dose of radiotherapy | Patients | Primary endpoint | ypCR | Grade 3/4 toxicity | CRM+ | 3yr-LR | 3yr-DFS | 3yr-OS | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACCORD | 2010 France | Cape (800 mg/m$^2$) | 45 Gy | 299 | ypCR | 13.9% | 11% | 19.3% | 6.1% | 67.9% | 87.6% | Administration of oxaliplatin and RT is not recommended. |
| | | Cape (800 mg/m$^2$)+ L-OHP (50 mg/m$^2$) | 50 Gy | 299 | | 19.2% (p=0.09) | 25% (p<0.001) | 9.9% (p=0.02) | 4.4% (HR, unknown) | 72.7% (0.88, 0.65-1.18)* | 88.3% (0.94; 0.59 to 1.48)* | |
| STAR-01 | 2011 Italy | 5-FU (225 mg/m$^2$/day) | 50.4 Gy | 379 | OS | 16% | 8% | 7% | — | — | — | Increase the toxicity without affecting primary tumor response. |
| | | 5-FU (225 mg/m$^2$/day)+ L-OHP (60 mg/m$^2$) | 50.4 Gy | 368 | | 16% (p=0.904) | 24% (p<0.01) | 4% (p=0.239) | — | — | — | |
| CAO/ARO-04 | 2012 Germany | 5-FU (1000 mg/m$^2$/day) | 50.4 Gy | 623 | DFS | 13% | 35% | 95% (R1+2) | | 71.2%- | 0 | Inclusion of oxaliplatin was feasible. The regimen can be deemed as a new treatment option. |
| | | 5-FU (1000 mg/m$^2$/day)+ L-OHP (50 mg/m$^2$) | 50.4 Gy | 613 | | 17% (p=0.038) | 36% | 94% (R1+2) | | 75.9% (HR, 0.79; p=0.03) | — | |
| NSABP R04 | 2014 USA | 5-Fu (225mg/m$^2$/day) or Cape (825mg/m$^2$) | 50.5-55.8 Gy | 636 | 3-yrLR | 17.8% | 6.9% | — | 12.1% (3-yr) | 64.2% (5-yr) | 79.0% (5-yr) | Auditioning oxaliplatin did not improve surgical outcomes but added significant toxicity. |
| | | 5-Fu (225mg/m$^2$/day) or Cape (825mg/m$^2$)+ L-OHP (50mg/m$^2$) | 50.5-55.8 Gy | 640 | | 19.5% (p=0.42) | 16.5% (p<0.01) | — | 11.2% (HR, 0.94; p=0.70) | 69.2% (HR, 0.91; p=0.34) | 81.3% (HR, 0.89; p=0.38) | |
| FOWARC | 2016 China | de Gramont regimen | 46-50.4 Gy | 155 | DFS | 12% (1) | 12.9%$^{\dagger}$ 7.7%$^{\dagger\dagger}$ 14.1%$^{\dagger\dagger\dagger}$ | 9.2% (R1+2) | — | — | — | mFOLFOX6-based preoperative chemoradiotherapy results in a higher pCR rate than fluorouracil-based treatment. |
| | | mFOLFOX | 46-50.4 Gy | 157 | | 21% (0.43; 0.24 to 0.78)* | 19.0%$^{\dagger}$ 14.5%$^{\dagger\dagger}$ 20.3%$^{\dagger\dagger\dagger}$ | 10.1% (R1+2) | — | — | — | |
| | | mFOLFOX | — | 163 | | 4% (2.31, 1.04-5.12)* | 5.7%$^{\dagger}$ 7.3%$^{\dagger\dagger}$ 0%$^{\dagger\dagger\dagger}$ | 10.6% (R1+2) | — | — | — | |

Cape: Capecitabine, L-OHP: Oxaliplatin, 5-FU: Fluorouracil, de Gramont regimen: leucovorin 400 mg/m$^2$ intravenously followed by fluorouracil 400 mg/m$^2$ intravenously and fluorouracil 2.4 g/m$^2$ by 48-h continuous intravenous infusion, mFOLFOX: de Gramont regimen plus oxaliplatin 85 mg/m$^2$ intravenously on day 1, ypCR: yp pathological complete response, CRM+: positive circumferential resection margin, 3-yrLR: 3-year local recurrence, 3-yrDFS: 3-year disease-free survival, 3-yrOS: 3-year overall survival, Hazard rate (HR): 95% confidence interval (C.I), $^{\dagger}$: Leukopenia, $^{\dagger\dagger}$: Diarrhea, $^{\dagger\dagger\dagger}$: Radiation dermatitis

**Table 2.** Phase II Trials Adding CPT-11 to Preoperative Chemoradiotherapy in Rectal Cancer

| Time country | Regimen | Dose of radiotherapy | Patients | ypCR | Grade 3/4 toxicity | 3yr-LR | 3yr-DFS | 3yr-OS |
|---|---|---|---|---|---|---|---|---|
| 2007 Germany | Cape (1000 mg/ $m^2$) CPT-11 (50 mg/$m^2$) | 50.4 Gy | 36 | 15% | 25% (leukocyto-penia only) | | | 80% |
| 2010 Korea | S-1 (70 mg/$m^2$) CPT-11 (40 mg/$m^2$) | 50.4 Gy | 43 | 21% | 7% | 9.5% | 72.1% | 94.3% |
| 2011 Japan | S-1 (80 mg/$m^2$) CPT-11 (80 mg/$m^2$) †Third course is only RT | 45 Gy | 67 | 34.7% | 9% | — | — | — |
| 2011 Korea | Cape (1650 mg/$m^2$) CPT-11 (40 mg/$m^2$) | 45 Gy | 48 | 25% | 14.6% | | 75.0% | 93.6% |
| 2015 Korea (Randomized phase II) | 5-FU (400 mg/$m^2$) leucovorin (20 mg/$m^2$) | 45-50.4 Gy | 66 | 16.7% | 1.4% | | 76.6.% | |
| | S-1 (35 mg/$m^2$) CPT-11 (40 mg/$m^2$) | 45-50.4 Gy | 67 | 25.8% (p=0.246) | 7% (p=0.095) | | 79.7% (p=0.896) | |

Cape: Capecitabine, 5-Fu: Fluorouracil, ypCR: yp pathological complete response, CRM+: positive circumferential resection margin, 3-yrLR: 3-year local recurrence, 3-yrDFS: 3-year disease-free survival, 3-yrOS: 3-year overall survival

CPT-11 as a radiosensitizer, although five phase II trials on the subject have been published[14,41-44]. Sato noted the usefulness of adding CPT-11, reporting a pCR rate of 34.7% and Grade 3 or 4 event rate of 9%[14]. Shin demonstrated a pCR rate of 21%, and only 3 of 42 patients (7%) had sepsis or septic shock[42]. In 2015 in Korea, a randomized phase II trial compared preoperative CRT with 5-FU/leucovorin or S-1/CPT-11. S-1/CPT-11-based CRT did not increase the pCR rate, but it did increase the rate of acute toxicities compared with standard 5-FU treatment[44]. Further studies are needed to confirm the usefulness of CPT-11 as a radiosensitizer.

*c) Bevacizumab*

No phase III trials have assessed the effect of adding bevacizumab, although several phase II trials on the subject have been published. Sadahiro demonstrated the outcomes of preoperative concurrent CRT with S-1 plus bevacizumab and found that adding bevacizumab to S-1 clearly increased the incidence of wound-related complications with no distinct enhancement of tumor response[45]. Dellas investigated the usefulness of preoperative radiotherapy with concurrent bevacizumab, capecitabine, and oxaliplatin and found that the addition of bevacizumab and oxaliplatin to preoperative CRT with capecitabine was well-tolerated and did not increase the perioperative morbidity or mortality[46]. However, the pCR rate was not improved in comparison to other trials that used capecitabine or capecitabine/oxaliplatin in preoperative CRT. Taken together, these findings fail to demonstrate the usefulness of bevacizumab in CRT for rectal cancer.

*d) Cetuximab*

Fokas performed a prospective phase 1/2 study to assess the effect of cetuximab and found that the addition of cetuximab did not improve the local control or recurrence rate[47]. In addition, Deutsch conducted the ACCORD 16 phase II trial to evaluate the objective response rate following the combination of conventional CRT with cetuximab in locally advanced anal canal carcinoma patients[48]. However, this trial was prematurely stopped due to serious adverse events, resulting in the conclusion that CRT plus cetuximab was unacceptably toxic in this population of patients. Taken together, these findings fail to demonstrate the usefulness of cetuximab in CRT for rectal cancer.

*e) Panitumumab*

Only one phase II trial has been published (from Switzerland), and the authors concluded that the addition of panitumumab to preoperative CRT in *KRAS* wild-type locally advanced rectal cancer patients resulted in a high near-pCR or pCR rate. However, the addition of panitumumab increased the toxicity[49].

From those outcomes, the standard treatment for rectal cancer is TME and preoperative CRT, using 5-FU as the radiosensitizer. Thus the development of new regimens for preoperative CRT is needed for further investigations.

### *2. Future treatment*

*2a. Induction chemotherapy followed by CRT (sequential regimen) (Table 3)*

The standard preoperative treatment for locally advanced rectal cancer is long-course CRT using a 5-FU-based chemosensitizer. However, T4 and/or N2-3 tumors have a high incidence of distant failure, even when treated with CRT, because CRT is considered as a local control treatment. As such, new strategies have been developed to resolve this issue, wherein induction chemotherapy is administered, followed by CRT and surgery (a sequential regimen) for locally advanced rectal cancer.

Seven reports have described the use of a sequential regimen for locally advanced rectal cancer (Table 3)[16-19,50,51]. The inclusion criteria for each study differed; therefore, the percentage of positive CRM, T-downstaging, N-downstaging, and pCR rate differed. However, a favorable pCR rate and T- and N-downstaging were consistently reported. Two randomized phase II trials compared the findings to those of standard-arm CRT followed by surgery, with the experimen-

**Table 3.** Previous Studies of Sequential Regimen for Rectal Cancer

| Authors, year of published | Study design | Inclusion criteria | Tumor height | Patients (n) | Preoperative therapy | Chemo regimen | Radiotherapy regimen | CRM+ | T-down staging | N-down staging | pCR rate | Adverse event Grade 3, 4 | Primary end point |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fernández-Martos C, 2010 | Randomized phase II | · CRM≦2 mm<br>· Lower third cT3 tumors<br>· Resectable cT4 tumors<br>· Any cT3N+ | ≦12 cm from anal verge | Standard arm 29 | CRT ⇒ Ope ⇒ Adjuvant chemo | (Adjuvant chemo) CAPOX; 4 course | 50.4 Gy with Capecitabine and Oxaliplatin | 13% (R1+R2) | 58% | — | 13% | Adjuvant chemo; 54%<br>CRT; 29% | pCR rate 13% v.s 14% N.S. |
| | | | | Experimental arm 28 | Induction chemo ⇒ CRT ⇒ Ope | CAPOX; 4 course | 50.4 Gy with Capecitabine and Oxaliplatin | 14% (R1+R2) | 43% | — | 14% | Induction Chemo; 19%<br>CRT; 23% | |
| Marechal, 2012 | Randomized phase II | · T2-4/N+M0 | ≦15 cm from anal verge | Standard arm 29 | CRT ⇒ Ope | — | 45 Gy with 5-Fu continuous infusion | 14% | 48% | 55% | 28% | 7% | ypT0-1N0 stage 34.5% v.s 32.1% N.S. |
| | | | | Experimental arm 28 | Induction chemo ⇒ CRT ⇒ Ope | FOLFOX 2 cycle | 45 Gy with 5-Fu continuous infusion | 4% | 46% | 43% | 26% | 36% | |
| Dewdney, 2012 | Randomized phase II | · Tumors within 1 mm of mesorectal fascia<br>· T3 tumors t or below levators<br>· Extramural extension≧5 mm<br>· T4 tumors<br>· Presence of extramural venous invasion | — | Standard arm 44 | Induction chemo ⇒ CRT ⇒ Ope | CAPOX; 4 course | 52.45 Gy with Capecitabine | 9% (R1+R2) | — | — | 9% | — | pCR rate 9% vs 11% N.S. |
| | | | | Experimental arm 46 | Induction chemo ⇒ CRT ⇒ Ope | CAPOX+ Cetuximab; 4 course | 52.45 Gy with Capecitabine and Cetuximab | 4% (R1+R2) | — | — | 11% | — | |
| Chua, 2010 | Phase II | · Tumour within 2 mm of mesorectal fascia<br>· Any T3 tumour at/below levatores<br>· T3c tumour at any other level ie tumour extends>5 mm into peri-rectal fat<br>· T4 tumour<br>· Any T stage with 4 or more involved lymph nodes | — | 105 | Induction chemo ⇒ CRT ⇒ Ope | CAPOX; 4 course | 54.0 Gy with Capecitabine | 2% | 53% | 59% | 20% | Induction Chemo; Diarrhoea 10%<br>Cardiac or thromboembolic toxic effect 9%<br>CRT: Skin 42% | — |
| Nogué M, 2011 | Phase II | · Lower third cT3 tumors<br>· Middle third of rectum with the CRM ≦2 mm<br>· Resectable cT4 tumors<br>· Any cT3N+tumors | ≦12 cm from anal verge | 47 | Induction chemo ⇒ CRT ⇒ Ope | Bevacizumab+ CAPOX; 4 course | 50.4 Gy with Bevacizumab and Capecitabine | 2% | — | — | 36% | Diarrhea 11%, neutropenia 6%, asthenia 4%, thrombocytopenia 4% | — |
| Beppu, 2016 | Phase II | · cT3 with mesorectal fascia involvement<br>· cT4 tumors<br>· Lateral lymph node swelling | ≦8 cm from anal verge | 20 | Induction chemo⇒short-course CRT ⇒ Ope | SOX±Cetuximab; 4 course | 25 Gy with S-1 | 20% | 70% | 80% | 10% | Induction chemo; Gastrointestinal 15%<br>Fatigue 10%<br>CRT: gastrontestinal 10% | pCR rate 10% |
| Bujko, 2016 | Phase III | · Fixed cT3 or cT4 cancer | ≦○ cm from anal verge | Standard arm 254 | CRT ⇒ Ope | — | 45 Gy with 5-Fu and leucovorin | 29% (R1+R2) | | | 16% | | R0 resection rates |
| | | | | Experimental arm 261 | Induction chemo⇒short-course RT ⇒ Ope | FOLFOX 3 cycle | 5×5 Gy | 23% (R1+R2) (p=0.07) | | | 12% (p=0.17) | | |

CRM: circumferential resection margin, CRT: chemoradiotherapy, pCR rate: pathological complete response rate

tal arm receiving induction chemotherapy followed by CRT and surgery. The sequential regimen was more favorable in terms of patient compliance and toxicity than the standard-arm of CRT. However, the primary endpoint of a decreased pCR rate or improved ypT0-1N0 status was not met[15,17]. In 2016, Bujko conducted a phase III trial to compare long-course oxaliplatin-based preoperative CRT versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer; they found that an improved overall survival and lower acute toxicity favored the 5 × 5 Gy schedule with consolidation chemotherapy. However, the primary endpoint of this study was the R0 resection rate, and no marked difference between the two arms was noted[51]. As described, concomitant therapies reduce the patient feasibility; therefore, this sequential regimen has the potential to improve the tolerance. The dose setting of chemotherapy drugs and assessment of treatment and side effects are needed to strengthen the evidence regarding the utility of sequential regimens.

*2b. Watch-and-wait policy*

In 2004, believing that all rectal cancer patients would prefer to avoid surgery, Habr-Gama first reported the watch-and-wait policy[52]. This strategy involves the observational management of rectal cancer patients with a cCR after CRT and has the benefit of avoiding a permanent stoma and anal or sexual dysfunction. However, a cCR does not always indicate a pCR, and until now, there has been no standard guideline regarding the selection of a patient, definition of a cCR, surveillance of recurrence, and long-term outcomes.

A total of 26 retrospective and prospective studies have investigated this approach, and nine have compared watch-and-wait policy groups with radical surgery groups, according to the review by Jun[53]. They concluded that, for rectal cancer patients achieving a cCR after CRT, a watch-and-wait policy with strict selection criteria, an appropriate follow-up schedule, and salvage treatments achieved outcomes at least as good as radical surgery. In 2016, the OnCoRe project provided evidence supporting the safety of the watch-and-wait policy: locally advanced rectal cancer patients were treated with CRT; those who had a cCR were given the option of the watch-and-wait policy, whereas those who did not have a cCR were offered surgical resection following CRT[54]. No marked difference in the 3-year disease-free survival (DFS) was observed between the groups (88% in the watch-and-wait policy group and 78% in the TME group). In addition, salvage TME surgery following watch-and-wait policy does not compromise the oncologic outcomes. These findings suggest that the watch-and-wait policy may be a viable option for rectal cancer in the near future. Further improvement in the cCR rate and optimization of surveillance are needed to get the best benefit for rectal cancer patients with this strategy.

*2c. Adjuvant chemotherapy for rectal cancer patients who received CRT*

As mentioned before, in Japan, CRT is still a minor treatment for locally advanced rectal cancer, and if selected, there is no standard postoperative treatment. In the US, the NCCN guidelines recommend adjuvant chemotherapy for locally advanced rectal cancer patients who receive CRT. In contrast, in Europe, most doctors do not perform adjuvant chemotherapy, based on the results of the five phase III randomized trials reviewed by Bujko et al[55-61]. Those trials failed to demonstrate a benefit of adjuvant chemotherapy compared with observation. Bujko summarized five randomized trials comparing a no adjuvant chemotherapy group versus 5-FU-based adjuvant chemotherapy groups, and none of the trials demonstrated a statistically significant benefit of CRT on the OS or DFS[62].

Four randomized trials compared the benefits between 5-FU-based adjuvant chemotherapy-alone groups and 5-FU chemotherapy groups with oxaliplatin addition. A meta-analysis of those four trials revealed no statistically significant differences in the findings. However, a phase II randomized controlled trial from Korea in 2014 showed that adjuvant FOLFOX improved DFS compared with fluorouracil plus leucovorin[63]. Indeed, over 95% of the FOLFOX group completed all eight planned cycles of adjuvant treatment without increasing the Grade 3 or 4 toxicity.

In summary, Bujko concluded that the use of adjuvant chemotherapy in rectal cancer patients receiving CRT is not based on strong scientific evidence. The characteristics of the patients who can expect to enjoy the benefits of 5-FU-based adjuvant chemotherapy with or without oxaliplatin are now being investigated.

*2d. The usefulness of lateral lymph node dissection following CRT*

Lateral lymph node metastasis is a major cause of local recurrence in rectal cancer, even when treated with CRT (without lateral lymphadenectomy). In Western countries, the presence of lateral lymph node metastasis is considered as a systemic disease, suggesting that these patients are not amenable to a surgical cure. However, recent reports from East Asia have demonstrated the usefulness of lateral lymphadenectomy for local control, even with CRT, for rectal cancer patients with lateral lymph node swelling. Ogura et al. demonstrated that even in rectal cancer patients with ≥7 mm swollen lateral lymph nodes, TME plus lateral lymphadenectomy following CRT did not compromise the oncologic outcomes compared with rectal cancer patients with no swelling and treated with TME following CRT[64]. These findings showed that not all patients with lateral lymph node swelling automatically have systemic disease. Kim et al. suggested that patients with lateral pelvic nodes responsive to preoperative CRT (≥5 mm lateral pelvic node pre-CRT but <5 mm post-CRT) could be expected to have good oncologic outcomes, including local control, compared to those with persistent lateral pelvic nodes (≥5 mm lateral pelvic node pre- and post-CRT)[21]. This study showed that the post-treatment stage is more useful for accurately predicting the outcomes than the clinical stage. In addition, reports from Korea have suggested that the decision to perform lateral lymph node dissection should be based on the lateral lymph

node response to CRT[65]. In contrast, Akiyoshi et al. showed that MRI before CRT was useful in predicting lateral lymph node metastasis and determining the indications for lateral lymphadenectomy[22]. Hence, the indications for lateral lymphadenectomy following CRT, which would consequently improve the local and systemic control, still remain controversial.

*2e. New or revised treatment strategies for lower rectal cancer*

At present, N+ or T3-4 rectal cancer patients are traditionally indicated for CRT; however, the ESMO guidelines classify T3 rectal cancer in more detail, based on the mesorectal extension depth (T3a, <1 mm; T3b, 1-5 mm; T3 c, 5-15 mm; T3d, >15 mm)[66]. More than half of all rectal cancers are T3 lesions, but they are classified as a single-stage category. Under these guidelines, cT3a(-b) with clear negative mesorectal fascia involvement according to MRI is not indicated for CRT, and primary surgery can be expected to achieve the same prognosis. However, a small number of clinical trials have demonstrated the usefulness of neoadjuvant chemotherapy without radiotherapy. Kamiya et al. conducted a phase II trial of perioperative oxaliplatin and capecitabine without radiotherapy for high-risk rectal cancer. They reported a good pCR rate (12.2%), but the T- and N-downstaging rates were likely to be insufficient[67]. Further studies are needed to clarify the indications for neoadjuvant chemotherapy without CRT.

Recently, several studies have begun to reevaluate the short-course regimen to resolve its drawbacks. The Stockholm III trial showed that a short-course regimen could be used to induce tumor downstaging by increasing the interval between radiation and surgery[68]. In addition, two randomized trials (a Polish study and an Australian study) showed roughly equivalent biological effectiveness between SRT and CRT for resectable rectal cancers[69,70]. Furthermore, a longer waiting period was shown to facilitate the planning of concomitant chemotherapy with a short-course regimen and a high rate of sphincter preservation[71]. Prospective studies are needed to strengthen the available evidence.

Conflicts of Interest

There are no conflicts of interest.

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