

Chemoradiotherapy for Local Recurrence of Rectal Cancer: A Single Center Study of 18 Patients

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Abstract. *Background/Aim:* When possible, surgical resection is recommended for local recurrence after resection of colorectal cancer. In unresectable cases, chemotherapy is usually indicated, although the success of chemoradiotherapy (CRT) in this setting is unclear. *Patients and Methods:* We retrospectively reviewed the treatment outcomes of 18 patients who received CRT for unresectable local recurrence after radical colorectal cancer surgery at our hospital between January 2000 and May 2016. *Results:* Of these 18 patients, three experienced complete response and four experienced partial response, resulting in a 39% overall response. With a median follow-up time of 42 months, the 5-year progression-free survival and overall survival were 34.8% and 54.4%, respectively; associated with a median local failure-free survival time of 40.9 months. Two of the three patients that underwent CRT remained local failure free for 5 years. *Conclusion:* CRT for local recurrence of rectal cancer without distant metastasis produces similar overall survival rates and local control as conventional surgical resection.

Despite significant advances in the multidisciplinary management of primary rectal cancer, local recurrence still develops. Local recurrence rates after surgery alone in patients with rectal cancer range between 5–10% (1). In addition, preoperative chemoradiotherapy (CRT) has been

associated with a pathological complete response in 15–20% of treated patients (2–5). The recommended therapeutic strategy for local recurrence of rectal cancer is surgical resection, if microscopically complete (R0) resection is possible. The 5-year survival rate after surgery in patients with local recurrence is 20–40% (6–8). However, the decision to perform curative surgery is made difficult by several factors: recurrence pattern, involvement of adjacent organs, medical unfitness, or patients' refusal due to the considerable risk of morbidity and mortality.

Radiotherapy (RT) for local recurrence of rectal cancer is a demonstrated effective treatment; it can also control symptoms such as pain. Recently, the ability of CRT using various anticancer drugs to improve treatment outcomes has been investigated. In a randomized controlled study of unresectable T4 rectal cancer or local recurrence of rectal cancer, 5-fluorouracil (5-FU)/leucovorin administered concurrently with radiation therapy was superior to RT alone with regard to local control, cancer-specific survival, and overall survival (9). This was despite the apparently higher toxicity associated with CRT. For local recurrence of rectal cancer, it is therefore considered that CRT may provide better outcomes compared with RT alone, if patients have not been previously irradiated. However, there have been few previous reports on the outcome of CRT.

The objective of this retrospective study was to clarify the treatment outcomes of CRT in patients with local recurrence of rectal cancer, and explore any difference in outcomes according to the combined chemotherapy regimens.

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Key Words: Rectal cancer, local recurrence, chemoradiotherapy.

Patients and Methods

Patients. The subjects of this study were patients with local recurrence of rectal cancer treated with CRT between January 2000 and May 2016 with a curative intent at the National Cancer Center Hospital. The following data of the patients were collected by

reviewing the medical chart: age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), interval between surgery and recurrence, size of the recurrent lesions, adjuvant chemotherapy, and reasons for selecting CRT. Imaging examinations were repeated every 8 weeks after the initiation of treatment. In patients with measurable target lesions, the objective response rate (ORR) was assessed according to the response evaluation criteria in solid tumors (RECIST) version 1.1. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (NCI CTCAEv4.0). This study was reviewed and approved by the institutional ethics committee of the National Cancer Center.

Chemoradiotherapy regimens. All patients received external beam radiation (50 to 60 Gy) with concurrent chemotherapy such as 5-FU continuous infusion (ci), or S-1, weekly 5-FU ci plus oxaliplatin, modified FOLFOX6 (mFOLFOX). 5-FU ci regimen was a continuous infusion of 2500 mg/week mg/m² of 5-FU (7 days), repeated every week. S-1 was administered orally at the dose of 80 mg/m²/day. Weekly 5-FU ci plus oxaliplatin regimen consisted of intravenous infusion of 50 mg/m² of oxaliplatin (2 h) on day 1 and continuous infusion of 2,500 mg/week 5-FU (7 days), repeated every week. The mFOLFOX regimen consisted of intravenous infusion of 85 mg/m² of oxaliplatin (2 h), 200 mg/m² l-leucovorin (2 hours), and 400 mg/m² bolus 5-FU on day 1, followed by a continuous infusion of 2,400 mg/m² of 5-FU (46 h), repeated every 2 weeks. Chemotherapy started from the first day and was repeated to the last day of radiotherapy in all patients, and subsequent chemotherapy regimens were determined by each physician's discretion according to the efficacy and toxicities of CRT. Six patients continued to receive chemotherapy until disease progression after the completion of radiation therapy.

Statistical analysis. Overall survival (OS) was defined as the time from the initiation of CRT to death from any cause or censored at the last follow-up. Progression-free survival (PFS) was defined as the time from the initiation of CRT to disease progression or death from any cause. Patients without disease progression who were lost to follow-up were censored at the last observation. Local failure-free survival (LFS) was defined as the time from the initiation of CRT to local disease progression or death regardless of distant metastasis, and all other events were censored at the last follow-up. PFS, OS, and LFS were estimated using the Kaplan–Meier method, and compared using the log-rank test. All the statistical analyses were performed using the JMP version 3.0 software.

Results

Patient characteristics. Eighteen patients, who underwent CRT with a curative intent for local recurrence after radical resection of rectal cancer between January in 2000 and May in 2016 at this hospital, were identified as the subjects of this study. None of them had previously been treated with radiotherapy to the pelvis.

Patient characteristics are shown in Table I. The median age of the patients was 66 years (range=27-80 years) and the ECOG PS was PS 0 in six patients, PS 1 in 11 patients, and PS 2 in one. None of the patients had metastatic lesions, and all had only local recurrence. Ten had a history of

Table I. Patient characteristics.

	N=18	%
Age, median (range)	66	(27-80)
Gender		
Male	13	72.2
Female	5	27.8
Performance status		
0	6	33.3
1	11	61.1
2	1	5.6
Histology		
Adenocarcinoma	18	100
Adjuvant chemotherapy		
Yes	10	55.6
No	8	44.4
The median period of time between surgery and local recurrence (range)	17.5 months	(4-56)
Tumor size, median (range)	49 mm	(15-100)
Reasons for selecting CRT		
Unresectable disease	11	61.1
Advanced age	4	22.2
Complication	2	11.1
Patient's refusal of surgery	1	5.6

fluoropyrimidine-based adjuvant chemotherapy. The median period of time between surgery and local recurrence was 17.5 months (range=4-56 months). The reasons for selecting CRT as the salvage treatment for local recurrence were unresectable disease in 11 patients, advanced age in four, complications in two, and refusal of surgery in one.

Doses of radiation were 59.4 Gy in 16 patients, 50 Gy in one, and 60 Gy in one, considering the radiation field and concurrent chemotherapy regimens. Fourteen patients (78%) received 3D conformal radiation therapy, and four patients (22%) received intensity modulated radiation therapy. Concurrent chemotherapy regimens were 5-FU ci plus weekly oxaliplatin in ten patients (56%), modified FOLFOX6 in four (22%), 5-FU ci in two (11%), and S-1 in two (11%). All patients had measurable lesions.

Treatment outcome. Of these 18 patients, three patients achieved complete response (CR), resulting in a CR rate of 17%, and four patients experienced partial response (PR), indicating that the response rate was 39% (7/18). Ten patients experienced stable response (SD), and the disease control rate was 94% (17/18). With a median follow-up period of 42 months (range=5-81 months), the 5-year PFS rate was 34.8% (95%CI=13.6-64.5; Figure 1). Five patients were still alive without disease progression in July 2017. In the remaining patients, disease progression patterns were local failure in five patients, both local failure and distant metastasis in four patients (three lung metastasis and one

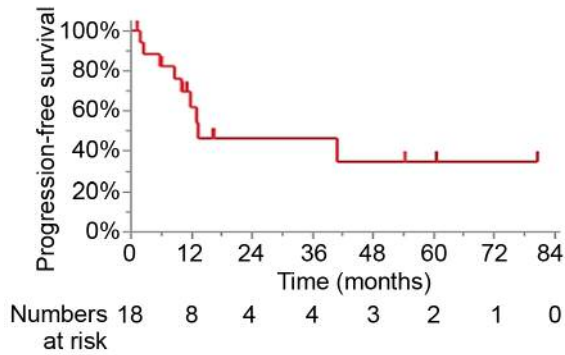


Figure 1. Progression-free survival curve calculated using the Kaplan–Meier method.

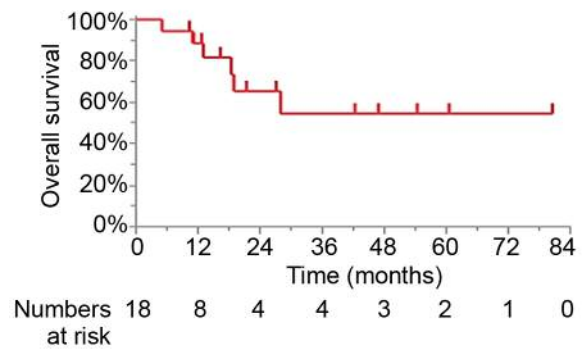


Figure 3. Overall survival curve calculated using the Kaplan–Meier method.

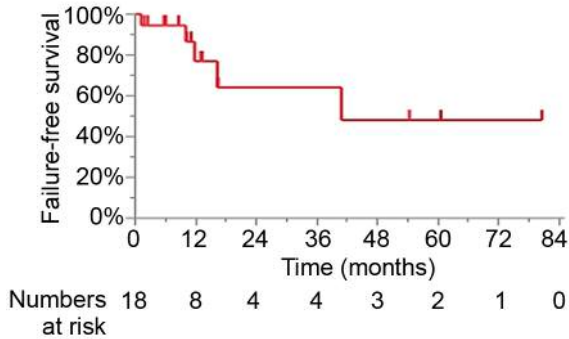


Figure 2. Local failure-free survival curve calculated using the Kaplan–Meier method.

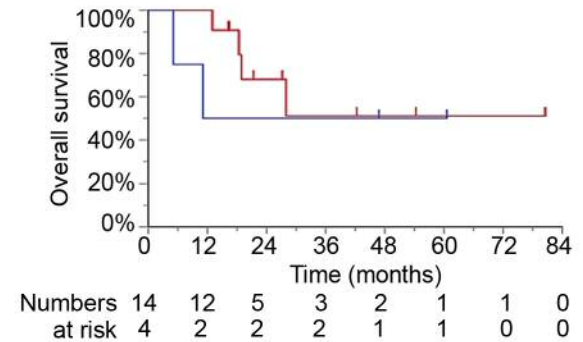


Figure 4. Overall survival curves using the Kaplan–Meier method for groups classified according to the treatment regimens.

mediastinal lymph node metastasis). The median LFS duration was 40.9 months (Figure 2). Of the three patients who achieved CR, two showed an LFS longer than 5 years. The 5-year OS rate was 54.4% (95%CI=27.3-79.2; Figure 3). There was no significant difference in 5-year OS between CRT using doublet chemotherapy and 5-FU-based monotherapy (51.1% vs. 50.0% for doublet regimen and monotherapy groups, respectively; $p=0.50$) (Figure 4).

Adverse events. Grade 3 or higher hematological toxicities were observed in three patients (17%): white blood cell count decreased in one patient and neutrophil count decreased in two. Grade 3 or higher non-hematological toxicities were observed in five patients (28%): diarrhea in three patients, stomatitis in one, and allergy in one. No severe late toxicity was observed during follow-up.

Three cases achieving CR. Case 1: A 53-year-old female had undergone transanal local resection for rectal cancer (cT1N0M0). She received adjuvant chemotherapy with

tegafur/uracil (UFT) and oral leucovorin for 6 months. Four years after surgery, pelvic CT scans revealed a 5-cm mass anterior to the sacrum. Weekly 5-FU ci plus oxaliplatin were delivered concurrently with RT (total dose 59.4 Gy) which was given to the pelvic lesion. 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) showed no uptake after CRT, and LFS was 81 months (Figure 5a).

Case 2: A 50-year-old male had undergone a low anterior resection (D2) for lower rectal cancer (cT1N0M0). He did not receive adjuvant chemotherapy. Nine months after surgery, colonoscopy revealed a 3-cm mass in the anastomosis. S-1 was delivered concurrently with RT (total dose 59.4 Gy). He experienced CR. However, thirteen months after CRT (Figure 5b), he was diagnosed with mediastinal lymph node metastases.

Case 3: A 75-year-old male had undergone a low anterior resection (D2) for lower rectal cancer (cT1N0M0). He took capecitabine for 6 months as adjuvant chemotherapy. Eighteen months after surgery, CT revealed a 2-cm mass in the lateral site of the pelvis. S-1 was delivered concurrently

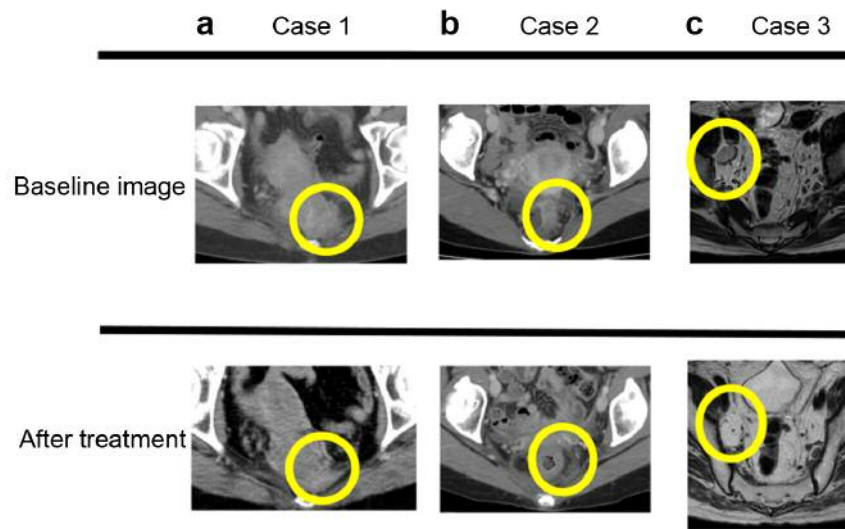


Figure 5. CT or MRI scan images of patients who achieved complete response.

with RT (total dose 59.4 Gy). He experienced CR and obtained LFS for 5 years (Figure 5c).

Discussion

There is no consensus regarding the treatment modality for local recurrence of rectal cancer. Although radical resection remains the first choice with a potential for cure, only approximately 20-40% of patients with recurrent rectal cancer are eligible for R0 resection (10-12). For patients who are not eligible, Bhanu *et al.* reported that there was no significant difference in long-term survival between R2 resection and those treated with non-surgical modalities (13). Thus, if curative resection (R0) cannot be performed, surgical resection is not expected to have a superior benefit. At this stage in the treatment of patients, radiation therapy and systemic chemotherapy alone or in combination should be taken into consideration (14, 15). In this retrospective study, we investigated the efficacy of CRT for the treatment of local recurrence of rectal cancer without distant metastasis. In our clinical experience, the response rate was 39% (7/18), and disease control rate was 94% (17/18); no severe adverse events were observed. Furthermore, CR was observed in 3 of 18 patients (16.7%), two of whom had LFS of more than 5 years.

The addition of 5-FU is reported to promote longer survival than RT alone for locally unresectable rectal cancer (16, 17). Furthermore, Ito *et al.* reported that CRT (continuous infusion of 5-FU+RT) was more effective than RT alone in 30 patients with local recurrent rectal cancer (18). The treatment outcomes resulted in a response rate of 31%, a disease control rate of 100%, and a median OS

period of 15.1 months, with manageable toxicities. Their report also showed an increase in the median OS of patients treated with CRT compared with RT alone (median survival time 9.3 months). Furthermore, CRT was effective for pain relief, and 5-FU based regimens were confirmed to be effective and safe. In comparison with their report on CRT, our result showed comparable survival effects of CRT. Median OS in our study was not reached, and the survival in our study was more favorable than the CRT group in Ito's study. This difference in efficacy between the Ito study and our current report may be due to the differences in the chemotherapeutic regimens and radiation therapy. Specifically, 5-FU alone and a median total dose of 50 Gy were evaluated by Ito *et al.* whereas several types of chemotherapy regimens, including oxaliplatin and a median total dose of 60 Gy, were examined in our study.

Since oxaliplatin was introduced into clinical practice, substantial progress has been made in chemotherapy of colorectal cancer. Chemotherapy with oxaliplatin combined with 5-FU, such as the FOLFOX regimen, is more effective and has become the standard treatment for advanced stage colorectal cancer (19, 20). Furthermore, preoperative CRT using an oxaliplatin-containing regimen for locally advanced rectal cancer showed a high success rate with toxicity within tolerable limits (21, 22). Among previous studies on CRT that incorporated oxaliplatin-containing regimen for recurrent rectal cancer, Hu *et al.* compared CRT [FOLFOX4+three-dimensional conformal radiotherapy (3-DCRT) and RT]. Patients in the CRT group had a significantly higher 2-year survival rate, with a substantially higher response rate (56% vs. 40%) (23). You *et al.* also assessed the outcome of concurrent CRT using oxaliplatin (oxaliplatin+pelvic

irradiation) in 96 patients with locally recurrent rectal cancer, and reported a CR rate of 14% and a PR rate of 61% (24). Cai *et al*. reported a CR rate of 5.6% following CRT with capecitabine and irinotecan with intensity modulated radiation therapy (IMRT) (45 Gy) associated with a 3-year survival rate of 36.5%; the 3-year local progression-free survival rate was 33.9% after a median follow-up of 31 months. As for adverse events, grade 4 leukopenia was 4.8%, grade 3 diarrhea was 22.5%, and toxicity was within a permissible range (25). Although CRT using doublet chemotherapy regimens for locally recurrent rectal cancer improved local control as well as survival rates in the above-mentioned reports, there was no significant difference in overall survival between CRT in the doublet regimen group and that of the 5-FU-based regimen group in our study. Possible explanations for this result are differences in patients' backgrounds and the limited number of patients in our study.

This study has several limitations. First, we only evaluated a small number of patients. Second, many of the patients were censored cases, which may have led to overestimation of the OS results. Third, the observation period of patients treated with the modified FOLFOX6+RT regimen was relatively short. Despite these limitations, our study suggests that CRT for patients with local recurrence of rectal cancer is an efficacious treatment modality that provides local control and improves survival rates.

In conclusion, CRT for local recurrence of rectal cancer without distant metastasis may have a meaningful survival benefit and a relatively manageable toxicity profile in clinical practice. Further research on a large population is needed in order to elucidate the treatment outcome of CRT for local recurrent rectal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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