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Original Research Article

Adjuvant Chemotherapy after Neoadjuvant Chemotherapy and Long-term Outcomes of CAPOX Plus Bevacizumab Followed by TME for High-risk Localized Rectal Cancer

Junichi Nishimura[1)], Junichi Hasegawa[2)], Shingo Noura[2)], Kimimasa Ikeda[3)], Masayoshi Yasui[1)], Takamichi Komori[4)], Masaki Tsujie[5)], Keigo Yasumasa[6)], Tatsushi Shingai[7)], Mamoru Uemura[8)], Taishi Hata[8)], Chu Matsuda[8)], Tsunekazu Mizushima[8)], Masataka Ikeda[9)], Yuichiro Doki[8)] and Masaki Mori[10)]

1) Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan
2) Department of Surgery, Osaka Rosai Hospital, Sakai, Japan
3) Department of Surgery, Minoh City Hospital, Minoh, Japan
4) Department of Surgery, Osaka General Medical Center, Osaka, Japan
5) Department of Surgery, Sakai City Medical Center, Sakai, Japan
6) Department of Surgery, JCHO Osaka Hospital, Osaka, Japan
7) Department of Surgery, Saiseikai Senri Hospital, Suita, Japan
8) Department of Gastroenterological Surgery, Osaka University, Suita, Japan
9) Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka, Japan
10) Department of Surgery and Science, Kyushu University, Fukuoka, Japan

Abstract

Objectives: We previously reported the feasibility of neoadjuvant capecitabine and oxaliplatin plus bevacizumab as a treatment for locally advanced rectal cancer (UMIN000003219). The aim of this study is to investigate the prognostic relevance of neoadjuvant chemotherapy followed by total mesorectal resection (TME).

Methods: Twenty-five patients of our prior multicenter prospective study of neoadjuvant chemotherapy followed by TME enrolled to this study. We analyzed the adjuvant chemotherapy regimen, and the duration between surgery and initial chemotherapy treatment. Five-year progression-free survival and overall survival were estimated using the Kaplan-Meier method.

Results: Among survivors, the median follow-up time was 66 months. Recurrence occurred in six patients, all of whom had suboptimal tumor regression after neoadjuvant chemotherapy. Five patients died from other causes. The rate of local recurrence and distant metastasis was 17.4% and 8.7%, respectively. Five-year progression-free survival was 70.0%, and 5 year overall survival was 84.0%.

Conclusions: We report the long-term survival of patients who received neoadjuvant chemotherapy without radiation followed by TME, revealing a generally favorable prognosis.

Keywords

rectal cancer, neoadjuvant chemotherapy, long-term survival, CapeOX, bevacizmab

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Corresponding author: Junichi Nishimura, jnishimura@gesurg.med.osaka-u.ac.jp
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Introduction

Locally advanced rectal cancer has a poor prognosis and constitutes a substantial health problem. In Western countries, the standard treatment is preoperative chemoradiation therapy (CRT) combined with total mesorectal excision (TME), which has been evaluated in several clinical studies. In Japan, the current standard treatment for locally advanced rectal cancer is TME or tumor-specific mesorectal excision (TSME) followed by adjuvant chemotherapy (CTx).

In recent years, there have been advancements in CTx methods for colorectal cancer, including new anticancer agents and targeted biological drugs. Several current guidelines indicate that the best adjuvant chemotherapy regimen includes oxaliplatin and fluoropyrimidine-based chemotherapy. We previously reported the feasibility of administering CAPOX + bevacizumab (BV) as treatment for high-risk localized rectal cancer[1]. In recent years, several clinical trials have demonstrated the efficacy of oxaliplatin-based chemotherapy without RT for locally advanced rectal cancer[2-5]. However, few reports have examined postoperative treatment including adjuvant chemotherapy and long-term survival[6].

In our present study, we assessed the long-term treatment outcomes of patients with locally advanced rectal cancer who were treated with preoperative CAPOX + BV without radiation.

Methods

The primary goal of this study was to update survival data from our previous investigation[1]. This study was approved by the ethics committees at each involved institution and was conducted in accordance with the declaration of Helsinki and all of its amendments, with the aim of offering the greatest protection to the patients.

Patients and treatment

Eligible patients were 20 to 75 years of age and had resectable T4 rectal cancer or nodes positive on magnetic resonance imaging. The protocol of patient treatment was described in the previous report[1]. In brief, patients received CAPOX + BV neoadjuvant CTx before undergoing surgery. Neoadjuvant CTx was administered for four cycles, with the fourth cycle of therapy excluding BV. Our previous study enrolled 25 cases, including 23 patients treated with TME/TSME (UMIN000003219). We defined pCR and near-pCR as we described before[1]. In brief, the complete absence of viable tumor cells in the resected specimen (100% response rate) was defined as a pathological complete response (pCR), and a response rate of ≥95% that was not a pCR was defined as a near-complete response (near-pCR). pCR and near-pCR were defined as favorable tumor regression[7]. After surgery, the decision of whether to administer adjuvant CTx was made by the attending physician in the previous study. For our present study, we recorded each patient's chemotherapy regimen, duration between surgery and chemotherapy, duration of oxaliplatin treatment, and any adverse events during adjuvant chemotherapy. Patients were evaluated and assessed for relapse every 6 months for approximately 5 years or until death.

Statistical analysis

We performed per-protocol analysis. Categorical variables were described using frequencies. Living patients were censored at last follow-up. Overall survival (OS) was calculated from the date of enrollment to the date of death from any cause, and progression-free survival (PFS) was defined as the time from surgery to relapse. The Kaplan-Meier method was used to estimate time-to-event endpoints.

Results

Adjuvant chemotherapy

Of the 25 patients in our previous study, 23 underwent curative resection. This group had a median age of 63 years (range, 37-75 years) and included 16 male and 7 female patients (Table 1). Lateral lymph node dissection was performed by unilateral in three patients and bilateral in seven patients. The ypStage was stage 0 (pCR) in one patient, stage I in four patients, stage IIA in nine patients, stage IIB in two patients, stage IIC in one patient, stage IIIA in one patient, stage IIIB in three patients, and stage IIIC in one patient. The demographic and clinicopathological characteristics of the patients at baseline and before surgery was described before[1].

Twelve patients (52.2%) received adjuvant chemotherapy (Table 2), with the chemotherapy regimen being CAPOX in 10 patients, capecitabine in one patient, and UFT/LV in one patient. The ypStage who received adjuvant chemotherapy was stage 0 (pCR) in one patient, stage I in three patients, stage IIA in four patients, stage IIB in one patient, and stage IIIB in two patients. Patients who did not receive adjuvant chemotherapy were rejected by 10 patients and StageI by one patient. The median duration from surgery to adjuvant chemotherapy was 57 days (range, 30-68 days). All adjuvant chemotherapy regimens were planned to last 3 months. One patient who underwent CAPOX therapy received three courses of adjuvant chemotherapy and refused one more course, such that the rate of completion of adjuvant chemotherapy with the CAPOX regimen was 90% (nine patients of 10) and 39.1% in all patients (nine patients of 23 patients). We assessed adverse events occurring during adjuvant chemotherapy. No patient who received adjuvant chemotherapy experienced any grade 4 adverse events. The major adverse

Table 1. Patient Background Data.

No. of patients		23
Age, years		
	Median	63
	Range	37-75
Sex, n (%)		
	Male	16 (69.6)
	Female	7 (30.4)
ypStage	0 (pCR)	1 (4.3)
	I	4 (17.4)
	IIA	9 (39.1)
	IIB	2 (8.7)
	IIC	1 (4.3)
	IIIA	1 (4.3)
	IIIB	3 (13.0)
	IIIC	1 (4.3)

Table 2. Adjuvant Chemotherapy.

Adjuvant chemotherapy	
Yes	12
ypStage I	1
ypStageIIA	5
ypStageIIB	2
ypStageIIC	1
ypStageIIIA	1
ypStageIIIB	1
ypStageIIIC	1
No	11
ypStage0 (pCR)	1
ypStageI	3
ypStageIIA	4
ypStageIIB	1
ypStageIIIB	2
Chemotherapy regimen	
CAPOX	10
Capecitabine	1
UFT/LV	1
Days between surgery and chemotherapy	57 (range, 40-68)
CAPOX completion rate	43.5%

Table 3. Adverse Events during Adjuvant Chemotherapy.

Adverse events (n = 12)	All grades, n (%)	G3, n (%)
Hematologic		
Neutropenia	7 (58.3)	4 (33.3)
Thrombocytopenia	4 (33.3)	1 (8.3)
CPK increase	1 (8.3)	1 (8.3)
Bilirubin increase	1 (8.3)	
	All grades, n (%)	G2, n (%)
Non-hematologic		
Peripheral neuropathy	4 (33.3)	3 (25.0)
Hand-foot syndrome	4 (33.3)	3 (25.0)
Malaise	3 (25.0)	
Nausea	1 (8.3)	
Anorexia	1 (8.3)	
Dysgeusia	1 (8.3)	

Table 4. Prognosis of Patients.

Follow-up period among survivors, median (range)	
66 months (58-79 months)	
Recurrence site (Include duplicates)	
Local*	4
Distant lymph node	1
Lung	1
Liver	1
Death	
Other disease	4

* Include one duplication of Local and Distant lymph node

events experienced were neutropenia, thrombocytopenia, increased CPK, peripheral neuropathy, and hand-foot syndrome (Table 3).

PFS and OS

The median follow-up time among the survivors was 66 months, with a range of 58-79 months (Table 4). Five patients exhibited favorable tumor regression, with histopathological findings indicating pCR or near-pCR, and none of these patients experienced recurrence (Table 5). Of the remaining 18 patients with suboptimal tumor regression, six patients (33%) experienced recurrence (26.1%), including local recurrence in one patient, lateral lymph node recurrence in two patients, multiple lymph node recurrence in one patient, lung metastasis in one patient, and liver metastasis in one patient. All relapses occurred within 2 years. Of the six patients who suffered recurrence, four had received surgical complete resection, and these four patients achieved a tumor-free condition after reoperation (Table 6). One patient who suffered lateral lymph node recurrence progressed to multiple lymph node recurrence including paraaortic lymph node recurrence. The patients who suffered only lateral lymph node dissection had not received lateral lymph node dissection at primary resection. Three patients died during the study period, including one death from cerebral hemorrhage, one from cardiovascular events, and one from primary lung cancer. To date, no deaths have occurred due to the original disease. Figure 1 shows the Kaplan-Meier curve of PFS and OS in the 25 patients who enrolled the previous study. Five year PFS was 70.0%, and 5 year OS was 84.0%.

Table 5. Tumor Regression and Recurrence.

	Total number	Recurrence	Local*	Distant lymph node	Lung	Liver
Favorable tumor regression						
pCR	1	0 (0%)				
Near-pCR	4	0 (0%)				
Suboptimal tumor regression	18	6 (33%)	4	1	1	1

* Include one duplication of Local and Distant Lymph node

Table 6. Patients' Demographics of Recurrence.

ypStage	Adjuvant chemotherapy	Recurrence site	Surgery for recurrence site
I	No	Local (Lateral LN) and Distant LN	
II	No	Local (anastomosis site)	Resection
II	CAPOX	Local (Lateral LN)	
II	No	Local (Lateral LN)	Lateral LN dissection
IIIA	CAPOX	Liver	Resection
IIIA	No	Lung	Resection

LN: lymph node

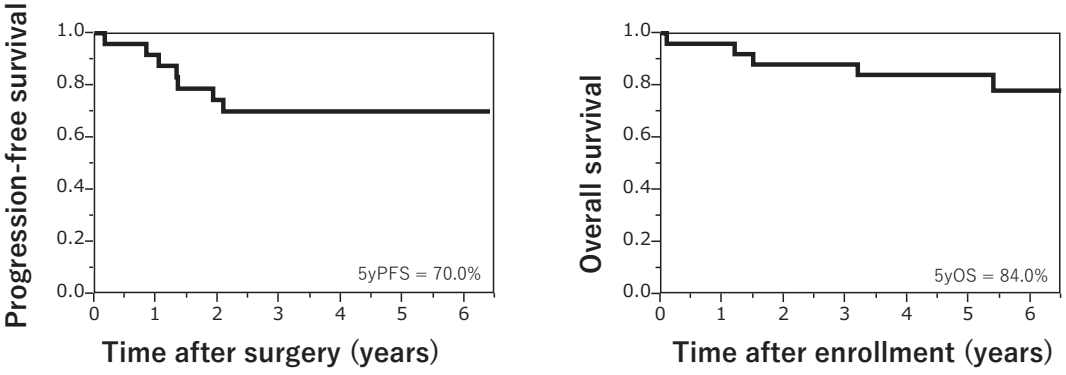

Figure 1. Progression-free survival and overall survival after enrollment.

Discussion

Here, we report the postoperative treatment after curative resection and long-term survival among patients with locally advanced rectal cancer who received neoadjuvant chemotherapy. Nearly half of patients underwent adjuvant chemotherapy. Patients who received 3 months of adjuvant chemotherapy underwent a total of 6 months of chemotherapy, whereas patients who did not receive adjuvant chemotherapy underwent a total of 3 months of chemotherapy including oxaliplatin and BV. Among the 10 patients treated with the CAPOX regimen, nine (90%) completed the planned treatment in full.

There are several advantages of neoadjuvant chemotherapy treatment. Neoadjuvant chemotherapy without radiation avoids the possibility of decreased anal function due to radiation to the anal sphincter. In this study, sphincter preservation was achieved in 60.9% of patients, and no patient had to retain their ileostomy or undergo stoma construction after resection. There remains a need for a randomized clinical trial to assess the advantage of neoadjuvant chemotherapy compared with neoadjuvant CRT with regard to preserving anal sphincter function.

Tumor shrinkage due to neoadjuvant chemotherapy may increase the rate of complete resection. We previously reported the achievement of R0 resection in all patients who underwent neoadjuvant chemotherapy for locally advanced rectal cancer[1], and other trials also report R0 resections in almost all patients under these circumstances[3-5,8]. With neoadjuvant CRT, pCR rates range from 11.4% to 27.5%[2,8-18]. On the other hand, the pCR rate with neoadjuvant chemotherapy was 4.3% in our present trial, and rates range from 6.6% to 25% in prior studies[3-5,8]. Thus, pCR rates are higher with neoadjuvant CRT than neoadjuvant chemotherapy. However, the R0 resection rate was not worse with neoadjuvant chemotherapy than with neoadjuvant CRT. These data suggest that neoadjuvant chemotherapy is an acceptable treatment strategy for locally advanced rectal can-

cer.

Some evidence suggests that chemotherapy including an adequate dose of oxaliplatin before resection might reduce the rate of distant metastatic recurrence[19]. Postoperative adjuvant chemotherapy with oxaliplatin improves the prognosis of colon cancer patients. However, recent clinical studies have attempted to improve treatment outcomes in locally advanced rectal cancer by using neoadjuvant CRT including oxaliplatin and have not found a better prognosis than with conventional CRT[12,16]. Moreover, no clinical trial has demonstrated a prognostic advantage of adjuvant chemotherapy for rectal cancer. It is unclear why adjuvant chemotherapy that improves the prognosis of colon cancer patients would not be effective as adjuvant chemotherapy in rectal cancer. One possibility is that the completion rate of adjuvant chemotherapy after neoadjuvant CRT followed by TME was lower to reduce recurrence including distant metastasis[6]. Other possibility is that this difference may be related to the distinct gene expression of colorectal cancer according to tumor location[20,21].

With regard to prior studies of neoadjuvant chemotherapy for locally advanced rectal cancer, Schrag et al.[4] reported 4 year DFS of 84%, and Patel et al.[22] reported 41 month DFS of 61%. In our present study, the 5 year PFS was 70.0%. Our study differed from prior studies with regard to patient background and treatment. For example, all cases in Schrag's trial had a T stage of T3, and Patel's study had a higher rate of incomplete neoadjuvant chemotherapy treatment. Our present results indicate that pCR and near-pCR patients had an improved prognosis. There remains a need for a large randomized clinical trial to compare the long-term prognosis of locally advanced rectal cancer with neoadjuvant chemotherapy versus CRT.

The local recurrence rate was 17.4% (4/23), including one case of duplicates of distant lymph node recurrence. The local recurrence site was anastomosis site in one patient and lateral lymph node in three patients. The lateral lymph node dissection was not done in two out of three patients who suffered lateral lymph node recurrence. The CRT or the lateral lymph node dissection for the lower rectal cancer patients of stage II/III might be improve the local recurrence rate. On the other hand, the hematogenous metastasis including lung and liver recurrence might be low (8.7%, 2/23) in this study. The distant recurrence rate in the study of CRT for rectal cancer was ranged from 17% to 27%[11,23]. Neoadjuvant chemotherapy might improve the hematogenous distant recurrence. Thus, neoadjuvant chemotherapy might be used to improve distant recurrence rate and CRT be used to improve local recurrence rate.

The present study has several limitations. As it was a single-arm trial with a small sample size, we could not compare neoadjuvant chemotherapy with standard therapy, and our results did not prove the effectiveness of neoadjuvant chemotherapy. Additionally, the adjuvant chemotherapy regimen was not regulated in this study.

In conclusion, here, we report the long-term results of CAPOX + BV as neoadjuvant chemotherapy, demonstrating a favorable prognosis. The local recurrence rate was high; however, the distant recurrence rate might be low. This study was a prospective single-arm clinical trial with a small sample size, and there remains a need for a larger clinical trial to verify the effectiveness of neoadjuvant chemotherapy for locally advanced rectal cancer.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Contributions to the design of the work: JN, JH, SN, KI, MY, TK, MT, KY, TS, MU, TH, CM, TM, MI, YD, and MM

Contributions to the acquisition of data for the work: JN, JH, SN, KI, MY, TK, MT, KY, TS, MU, TH, CM, and TM

Contributions to analysis, and interpretation of data for the work: JN, JH, MU, TH, CM, and TM

Drafting the work or revising it: JN, JH, SN, KI, MY, TK, MT, KY, TS, MU, TH, CM, TM, MI, YD, and MM

Approval by Institutional Review Board (IRB)

Approval code of IRB: 15464

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