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Reevaluation of Oral Adjuvant Chemotherapy for T3 Lower Rectal Cancer : A Multicenter Collaborative Retrospective Cohort Study

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ABSTRACT

Aim : This retrospective study evaluated the usefulness of oral adjuvant chemotherapy (OAC) for T3 lower rectal cancers without lateral lymph node metastasis.

Patients and Methods : The subjects were 110 patients who had T3 lower rectal cancer without lateral lymph node metastasis, were 80 years or younger, and had undergone curative resection at an affiliated hospital of The Jikei University School of Medicine from 2010 through 2014. No patients received preoperative chemoradiotherapy, and of the 47 patients with stage II cancer, none received postoperative chemotherapy. Of the 63 patients with stage III cancer, 47 received postoperative OAC and 16 received postoperative intensive oxaliplatin-based combination chemotherapy.

Results : The 5-year disease-free survival (DFS) rate of patients with stage II cancer (82.6%) was significantly higher than that of patients with stage III disease (63.1% ; $p = 0.033$). If patients with stage III cancer received intensive chemotherapy, their 5-year DFS rate (81.3%) was similar to that of patients with stage II cancer but was significantly decreased if they received OAC (58.2%, $p = 0.048$).

Conclusion : For patients with stage III lower rectal cancer, intensive postoperative oxaliplatin-based combination chemotherapy achieves a higher 5-year DFS rate than does OAC. Therefore, OAC is not suitable for these patients, even if lateral lymph node metastasis has not been detected.

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Key words : oral adjuvant chemotherapy, lower rectal cancer, intensive chemotherapy disease-free survival

INTRODUCTION

Postoperative adjuvant chemotherapy is a type of systemic chemotherapy that is performed after surgery to prevent recurrence and improve the prognosis of patients who have undergone R0 resection, which is defined as complete, curative resection with margins that are microscopically negative[1]. Systemic adjuvant chemotherapy is indicated in the Japanese Society for Cancer of the Colon and Rectum Guidelines 2010[2] as follows : (1) stage III colorectal cancer for which R0 resection has been performed ; (2) maintenance of the function of major organs, bone marrow, liver function, and renal function ; and (3) patients who have stage II colorectal cancer with a high risk of recurrence. The chemotherapeutic regimens paid for by the Japanese National Health Insurance system are as follows : (1) fluo-

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rouracil (5-FU) + levofolinate calcium (l-LV), (2) uracil and tegafur (UFT) + calcium folinate (LV), (3) capecitabine, and (4) infusional 5-FU and l-LV plus oxaliplatin (FOLFOX4 or mFOLFOX6). In principle, the recommended administration period is 6 months. At the affiliated hospitals of The Jikei University School of Medicine, patients with T3 rectal cancer undergo adjuvant chemotherapy according to the guidelines. However, the usefulness of oral adjuvant chemotherapy for treating T3 tumors of the lower rectum without lateral lymph node metastasis has not been elucidated. Therefore, to elucidate the usefulness of oral adjuvant chemotherapy for patients with such tumors, we performed the present retrospective study of the affiliated hospitals of The Jikei University School of Medicine.

Materials and Methods

Study protocol, patients, and surgery

The protocol of this retrospective study [30-249 (9270)] was approved by the Ethics Committee for Biomedical Research of the Jikei Institutional Review Board. The subjects were 110 patients who had T3 lower rectal cancer without lateral lymph node metastasis, were 80 years or younger, and had undergone curative resection at 4 affiliated hospitals of The Jikei University School of Medicine from 2010 through 2014 (Table 1). The pathological diagnosis was stage II cancer in 47 patients and stage III cancer in 63 patients. All patients underwent total mesorectal excision with bilateral autonomic nerve preservation without lateral pelvic lymph node dissection and did not receive preoperative chemoradiotherapy.

Table 1. Characteristics of all patients

Characteristic	Number of patients (n = 110)
Mean age (range), years	65.2 (36-80)
Sex, *n* (%)	
Male	69 (63)
Female	41 (37)
Mean tumor diameter (range), mm	56.8 (14-108)
Pathology, *n* (%)	
Well-differentiated adenocarcinoma	28 (26)
Moderately differentiated adenocarcinoma	73 (66)
Others	9 (8)
Lymphatic invasion, *n* (%)	
Negative	31 (28)
Positive	79 (72)
Venous invasion, *n* (%)	
Negative	36 (33)
Positive	74 (67)
Stage, *n* (%)	
II	47 (43)
III	63 (57)
Surgical procedure, *n* (%)	
Low anterior resection	65 (59)
Abdominoperineal resection	40 (36)
Intersphincteric resection	2 (2)
Hartmann operation	3 (3)
Surgical technique, *n* (%)	
Laparoscopic surgery	46 (42)
Open surgery	64 (58)
Recurrence site, *n* (%)	
Lung	20 (18)
Liver	10 (9)
Brain	2 (2)
Lymph node	2 (2)
Local	6 (5)

Postoperative chemotherapy

Of the 47 patients with stage II cancer, none received postoperative chemotherapy. However, of the 63 patient with stage III cancer, 47 received postoperative oral adjuvant chemotherapy for 6 months with oral S-1 (Taiho Pharmaceuticals Co., Ltd., Tokyo, Japan) or capecitabine (Xeloda ; Hoffmann-La Roche, Basel, Switzerland). The other 16 patients with stage III cancer received intensive postoperative chemotherapy for 6 months with the following oxaliplatin-based combination regimens : infusional 5-FU and folinic acid plus oxaliplatin (FOLFOX), S-1 plus oxaliplatin, and capecitabine plus oxaliplatin.

Postoperative follow-up

All patients were followed up after surgery for 5 years, and every 2 months underwent physical examinations, routine blood analyses, and serum measurements of carcinoembryonic antigen. Computed tomography was performed every 6 months or when the serum carcinoembryonic antigen level was higher than the reference level of 5.0 ng/ml. Colonoscopy was performed every year or when a stool sample was positive for blood. Positron emission tomography with or without computed tomography was occasionally performed to detect occult metastasis for patients who had equivocal conventional imaging studies.

Statistical analysis

The medical records of all patients were reviewed and classified according to the Japanese Classification of Colorectal Carcinoma[3]. A tumor that has invaded the subserosa is classified as T3. Disease-free survival (DFS) and the treatments received were compared among the patient groups. The DFS after surgery was examined with the Kaplan–Meier method and log-rank analysis.

Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-squared test was used to compare categorical data. To determine the variables affecting postoperative recurrence, 5 variables (age, sex, type of adjuvant chemotherapy, number of lymph node metastases, and surgical approach) were analyzed with the Cox proportional hazards regression. A p-value of less than 0.05 indicated significance. All data were analyzed with the software program IBM SPSS Statistics, version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

Comparison of DFS between stage II and stage III lower rectal cancer

Significant differences were identified in only lymphatic invasion (Table 2). The 5-year DFS rate was significantly higher for patients with stage II disease (82.6%) than for patients with stage III disease (63.1%, $p = 0.033$; Fig. 1).

Comparison of DFS between patients with stage III cancer receiving intensive or oral adjuvant chemotherapy

Among patients with stage III lower rectal cancer, significant differences regarding the type of postoperative adjuvant chemotherapy received were found in only the sites

Table 2. Characteristics of patients with stage II or stage III rectal cancer

Characteristic	Stage II ($n = 47$)	Stage III ($n = 63$)	p value
Mean age (range), years	65.2 (36–80)	64.7 (36–80)	0.595
Sex, *n* (%)			0.416
Male	27 (57)	42 (67)	
Female	20 (43)	21 (33)	
Mean tumor diameter (range), mm	55.4 (14–90)	57.8 (15–108)	0.670
Pathology, *n* (%)			0.426
Well-differentiated adenocarcinoma	13 (28)	15 (24)	
Moderately differentiated adenocarcinoma	31 (66)	42 (67)	
Others	3 (6)	6 (9)	
Lymphatic invasion, *n* (%)			0.005
Negative	20 (43)	11 (17)	
Positive	27 (57)	52 (83)	
Venous invasion, *n* (%)			0.543
Negative	17 (36)	19 (30)	
Positive	30 (64)	44 (70)	
Surgical procedure, *n* (%)			0.965
Low anterior resection	27 (58)	38 (60)	
Abdominoperineal resection	18 (38)	22 (35)	
Intersphincteric resection	1 (2)	1 (2)	
Hartmann operation	1 (2)	2 (3)	
Surgical technique, *n* (%)			0.242
Laparoscopic surgery	23 (49)	23 (37)	
Open surgery	24 (51)	40 (63)	
Recurrence site, *n* (%)			0.308
Lung	6 (13)	14 (22)	
Liver	2 (4)	8 (13)	
Brain	1 (2)	1 (2)	
Lymph node	0 (0)	2 (3)	
Local	0 (0)	6 (10)	

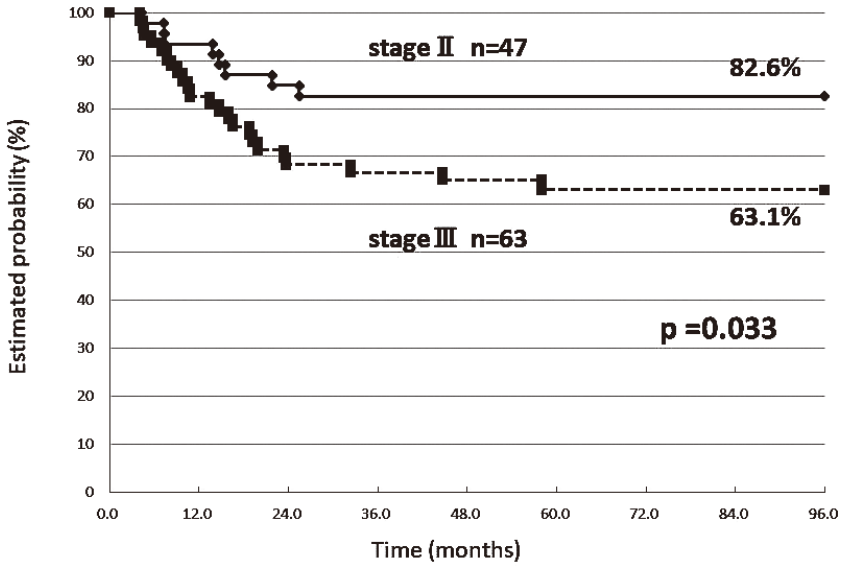

Fig. 1. Disease-free survival rates of patients with stage II or stage III rectal cancer

Table 3. Comparison of characteristics of intensive and oral adjuvant chemotherapy after surgery for stage III rectal cancer

Characteristic	Intensive therapy (n = 16)	Oral chemotherapy (n = 47)	p value
Mean age, years (range)	60.5 (36-77)	66.2 (40-80)	0.055
Sex, n (%)			0.682
Male	10 (63)	32 (68)	
Female	6 (37)	15 (32)	
Mean tumor diameter, mm (range)	66.9 (20-100)	54.8 (15-108)	0.051
Pathology, n (%)			0.592
Well-differentiated adenocarcinoma	5 (31)	10 (21)	
Moderately differentiated adenocarcinoma	9 (56)	33 (70)	
Others	2 (13)	4 (9)	
Lymphatic invasion, n (%)			0.590
Negative	4 (25)	7 (15)	
Positive	12 (75)	40 (85)	
Venous invasion, n (%)			0.403
Negative	3 (19)	16 (34)	
Positive	13 (81)	31 (66)	
Surgical procedure, n (%)			0.317
Low anterior resection	8 (50)	30 (64)	
Abdominoperineal resection	8 (50)	14 (30)	
Intersphincteric resection	0 (0)	1 (2)	
Hartmann operation	0 (0)	2 (4)	
Surgical technique, n (%)			1.000
Laparoscopic surgery	6 (38)	17 (36)	
Open surgery	10 (62)	30 (64)	
Recurrence site, n (%)			0.003
Lung	2 (13)	12 (26)	
Liver	2 (13)	6 (13)	
Brain	1 (6)	0 (0)	
Lymph node	0 (0)	2 (4)	
Local	0 (0)	6 (13)	

of recurrence (Table 3). Of the 16 patients who received intensive chemotherapy, neither local recurrence nor lymph node metastasis was identified, but among the 47 patients who received oral adjuvant chemotherapy, 6 (13%) had local recurrence and 2 (4%) had lymph node metastasis. The 5-year DFS rate of the patients who received intensive postoperative chemotherapy for stage III disease (81.3% ; Fig. 2) was similar to that of patients with stage II disease (82.6% ; Fig. 1) but was significantly greater than that of patients with stage III disease who received oral adjuvant chemotherapy (58.2%, $p = 0.048$).

Factors for postoperative recurrence in stage III

The only independent contributing factor for postoperative recurrence identified with Cox proportional hazards regression analysis was the type of adjuvant chemotherapy ($p = 0.049$). The risk of postoperative recurrence of patients who received intensive chemotherapy was approximately 40% of that of patients who received oral adjuvant chemotherapy (Table 4).

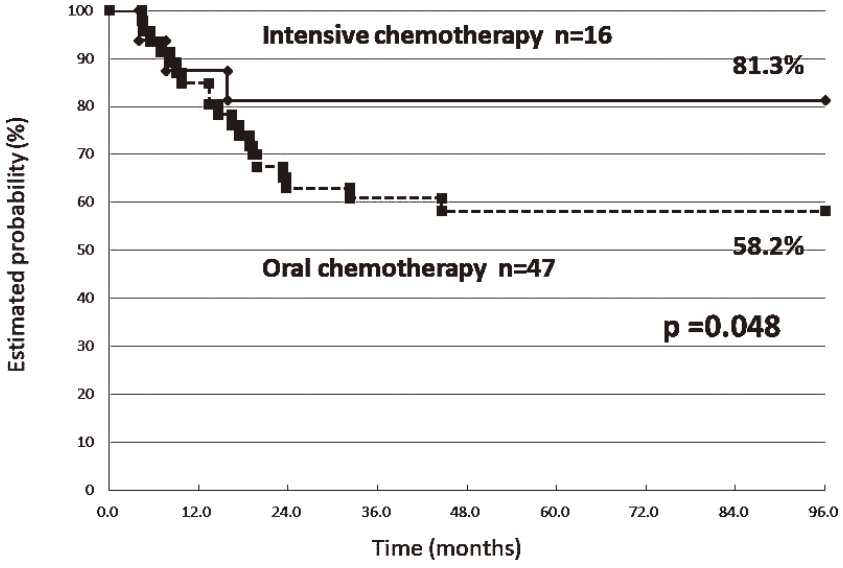

Fig. 2. Disease-free survival rates of patients with stage III rectal cancer who received postoperative intensive or oral adjuvant chemotherapy

Table 4. Multivariate analyses using the Cox proportional hazard model for postoperative recurrence

Variable	Hazard Ratio (95% confidence interval)	*P* value
Age (years)		
≥ 70	1.188 (0.508-2.782)	0.691
< 70	1	
Sex		
Female	1.179 (0.496-2.804)	0.709
Male	1	
Adjuvant chemotherapy		
Intensive chemotherapy	0.415 (0.117-0.967)	0.049
Oral chemotherapy	1	
Number of lymph node metastases		
≥ 4	1.151 (0.475-2.788)	0.755
< 4	1	
Surgical technique		
Laparoscopic surgery	0.599 (0.234-1.537)	0.287
Open surgery	1	

DISCUSSION

From 1990 through 2004, postoperative chemotherapy with leucovorin - modulated 5-FU (5-FU + l-LV) was the standard of care for patients with stage III colon cancer, based on the mortality rate was 26% lower with chemo + surgery than with surgery alone[4]. For adjuvant chemotherapy, effective alternatives to 5-FU + l-LV can be the oral fluoropyrimidines capecitabine and S-1. In a randomized phase III study, capecitabine achieved a DFS equivalent to that with bolus 5-FU + l-LV (Mayo Clinic regimen) and was associated with significantly fewer adverse events[5]. Furthermore, UFT + LV and capecitabine have shown noninferiority to 5-FU + l-LV[6], and S-1 has shown noninferiority to UFT + LV[7]. Thus, oral adjuvant chemotherapy has been considered the gold standard of care for patients with stage III colorectal cancer in Japan since 2000.

In 2004, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial demonstrated that the addition of oxaliplatin to 5-FU + l-LV improved both DFS and overall survival in patients with stage III colon cancer[8]. Oxaliplatin-based combination regimens, such as FOLFOX, S-1 plus oxaliplatin, and capecitabine plus oxaliplatin, have been considered the gold standard of adjuvant chemotherapy for stage III colorectal cancer in Japan since 2004. However, the usefulness of oral adjuvant chemotherapy for T3 lower rectal cancers without lateral lymph node metastasis has not been elucidated.

In the present study, the 5-year DFS of patients who received intensive oxaliplatin-based combination chemotherapy after surgery (81.3% ; Fig. 2) was similar to that of patients with stage II lower rectal cancer who received no adjuvant chemotherapy (82.6% ; Fig. 1). However, the 5-year DFS of patients with stage III cancer who received postoperative oral adjuvant chemotherapy was significantly lower (58.2%, $p = 0.048$; Fig. 2). Furthermore, the risk of postoperative recurrence with intensive chemotherapy was approximately 40% of that with oral adjuvant chemotherapy (Table 4). Several large-scale randomized controlled trials have found that, for patients with stage III colon cancer, oxaliplatin-based combination therapy significantly reduces the risk of recurrence and improves the outcome compared with 5-FU + l-LV, which was comparable to oral adjuvant chemotherapy[8,9].

Among patients who receive oxaliplatin combination therapy, the most common adverse event is sensory peripheral neuropathy, the incidence of which is greater than with oral adjuvant chemotherapy. However, the incidence of sensory peripheral neuropathy is significantly lower after 3 months than after 6 months[10]. However, the Short Course Oncology Therapy trial has found that the postoperative recurrence rate of a 3-month oxaliplatin combination therapy was similar to that of the 6-month administered, especially in patients with a low risk of recurrence. The 3-year DFS were also similar after 3 months or 6 months of administration[11]. The optimal oxaliplatin administration period as adjuvant therapy is still debated.

In conclusion, the present study has found that for patients with stage III lower rectal cancer the 5-year DFS rate after surgery is higher with oxaliplatin combination intensive chemotherapy than with oral adjuvant chemotherapy. Furthermore, oral adjuvant chemotherapy is not suitable as an adjuvant chemotherapy for patients with stage III lower rectal cancer, even if no lateral lymph node metastasis has been detected.

Conflict of Interest Statement

The authors have no conflicts of interest.

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