Reevaluation of Preoperative Chemoradiotherapy for Clinical T3 Lower Rectal Cancer: A Multicenter Collaborative Retrospective Clinical Study

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Abstract. *Aim: This study aimed to re-evaluate the usefulness of preoperative chemoradiotherapy for clinical T3 lower rectal cancers without lateral lymph node metastasis. Patients and Methods: Between 2010 and 2014, 132 patients with clinical T3 lower rectal cancer without lateral lymph node metastasis, 80 years of age or younger, who underwent curative resection at four Jikei University Hospitals were enrolled into this retrospective study. Of these, 22 patients received chemoradiotherapy (CRT) before surgery, 16 patients received intensive chemotherapy after surgery without preoperative CRT, and 94 patients underwent neither preoperative CRT nor intensive chemotherapy after surgery including 47 patients with postoperative oral chemotherapy for pathological diagnosis of stage III. Results: The 3-year disease-free survival (DFS) of the 22 patients who received preoperative CRT was 95.5%, whereas that of the 94 patients who received neither preoperative CRT nor intensive chemotherapy was 72.0% ($p=0.024$). However, there was no significant difference in 5-year DFS between the two groups. No significant difference was identified in DFS between the 22 patients who received preoperative CRT and the 16 patients who received intensive chemotherapy after surgery without preoperative CRT. Conclusion: Intensive chemotherapy after surgery seems to yield a similar prognosis to preoperative CRT in patients with clinical T3 lower rectal cancer without lateral lymph node metastasis.*

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Total mesorectal excision (TME) has been the worldwide gold-standard surgical procedure for rectal cancer (1). However, in Japan, TME plus lateral lymph node dissection without preoperative chemoradiotherapy (CRT) has been regarded as an optimal surgical procedure for advanced lower rectal cancer because of the reduced incidence of local recurrence or improved survival after those surgical procedures alone (2-8). In Western countries, TME plus preoperative CRT has been a standard treatment for locally advanced rectal cancer (9-16). However, the dose, duration, radiation target volumes, optimal concomitant agents, and outcomes remain controversial. This study aimed to re-evaluate the usefulness of preoperative CRT for clinical T3 lower rectal cancer without lateral lymph node metastasis.

Patients and Methods

The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol of this study [30-249(9270)]. Between 2010 and 2014, 132 patients with clinical T3 lower rectal cancer without lateral lymph node metastasis, 80 years of age or younger, who underwent curative resection at four Jikei University Hospitals were enrolled in this study. Of these patients, 22 received CRT before surgery, 16 received intensive chemotherapy after surgery without preoperative CRT, and 94 underwent neither preoperative CRT nor intensive chemotherapy (IC) after surgery, including 47 patients with postoperative oral chemotherapy for pathological diagnosis of stage III (Table I). All patients ($n=132$) underwent TME with bilateral autonomic nerve preservation without lateral pelvic lymph node dissection. Comparisons between disease-free survival (DFS) and the received treatments were retrospectively evaluated. The medical records of all patients were reviewed and classified according to the Japanese Classification of Colorectal Carcinoma (17). According to this classification, T3 corresponds to the invasion of the subserosa. Significant differences were identified in gender, mean tumor diameter, lymphatic invasion, stage, and surgical technique between the preoperative CRT group and the non-CRT group by postoperative evaluation (Table II).

Table I. Treatment strategies for lower rectal cancer used in the study population (n=132).

Treatment	n (%)
Preoperative chemoradiotherapy (CRT)	22 (17.0)
Postoperative intensive chemotherapy (IC)	16 (12.0)
Neither preoperative CRT nor postoperative IC	94 (71.0)
Oral adjuvant chemotherapy	47 (50.0)
Surgery alone	47 (50.0)

Lymph nodes detected by computed tomography (CT) with a diameter of more than 7 mm before CRT were regarded as metastatic lymph nodes (18).

Preoperative CRT. Radiotherapy was administered in fractions of 2 Gy per day, given 5 days per week for 4 weeks (total dose of 40 Gy). UFT (Taiho Pharmaceuticals Co. Ltd, Tokyo, Japan) (300 mg/m²/day) or capecitabine (Xeloda; Hoffmann-La Roche, Basel, Switzerland) (1600 mg/m²/day) was given orally on days 1 to 5, 8 to 12, 15 to 19, and 22 to 26 as additional chemotherapy. The treatment field of radiotherapy included perirectal lymph nodes and lateral lymph nodes.

Intensive chemotherapy after surgery. The intensive chemotherapy group (n=16) received oxaliplatin-based regimens [infusional 5-fluorouracil and folinic acid plus oxaliplatin (FOLFOX), S-1 (Taiho Pharmaceuticals Co. Ltd, Tokyo, Japan) plus oxaliplatin (SOX), capecitabine plus oxaliplatin (XELOX)] for 6 months after surgery.

Oral adjuvant chemotherapy after surgery. For 6 months after surgery, patients with stage III disease (n=47) received oral S-1 or capecitabine, whereas patients with stage II disease (n=47) received no adjuvant chemotherapy. Patients who had received preoperative CRT (n=22) received no adjuvant chemotherapy.

Treatment schedule. All patients were followed for 5 years; during this period, physical examinations, routine blood analyses, and serum CEA measurements were conducted every two months after surgery. CT was performed every 6 months or when a patient's serum CEA value was higher than the normal level of 5.0 ng/ml. Colonoscopy was performed every year or when a stool sample was positive for blood. Positron emission tomography (PET) or PET/CT was occasionally employed to detect occult metastasis for patients who had equivocal conventional imaging studies.

Statistical analysis. Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used for the comparison of continuous variables, and a chi-squared test was used for the comparison of categorical data. DFS after surgery was examined by the Kaplan-Meier method and by log-rank analysis. A *p*-value of less than 0.05 indicated significance. All data were analyzed with IBM SPSS Statistics, version 24.0 (IBM Japan, Ltd, Tokyo, Japan).

Results

Pathologic response to preoperative CRT. Preoperative CRT was successful in pathological T-downstaging 10/22 patients to smaller than T2. Pathologic complete response (pCR) was

Table II. Comparison of characteristics between preoperative chemoradiotherapy (CRT) group and non-CRT group.

Characteristic	CRT (–) (n=110)	CRT (+) (n=22)	<i>p</i> -Value
Mean age (range), years	65.2 (36-80)	63.0 (50-80)	0.293
Gender, n (%)			0.032
Male	69 (63)	19 (86)	
Female	41 (37)	3 (14)	
Mean tumor diameter (range), mm	56.8 (14-108)	35.4 (0-95)	<0.001
Pathology, n (%)			0.530
Well-differentiated adenocarcinoma	28 (26)	8 (36)	
Moderately-differentiated adenocarcinoma	73 (66)	13 (59)	
Others	9 (8)	1 (5)	
Lymphatic invasion, n(%)			0.005
Negative	31 (28)	13 (59)	
Positive	79 (72)	9 (41)	
Venous invasion, n (%)			0.046
Negative	36 (33)	12 (55)	
Positive	74 (67)	10 (45)	
Stage, n(%)			0.009
II	47 (43)	16 (73)	
III	63 (57)	6 (27)	
Surgical procedure, n (%)			0.857
Low anterior resection	65 (59)	14 (63)	
Abdominoperineal resection	40 (36)	7 (32)	
Intersphincteric resection	2 (2)	0 (0)	
Hartmann operation	3 (3)	1 (5)	
Surgical technique, n (%)			<0.001
Laparoscopic surgery	46 (42)	19 (86)	
Open surgery	64 (58)	3 (14)	
Recurrence site, n (%)			0.316
Lung	20 (18)	2 (9)	
Liver	10 (9)	1 (5)	
Brain	2 (2)	0 (0)	
Lymph node	2 (2)	0 (0)	
Local	7 (6)	0 (0)	

found in 2/22 patients. Pathologic lymph node metastasis was eradicated by preoperative CRT in 4 of 10 patients.

Comparison of DFS between the preoperative CRT and non-CRT groups without intensive adjuvant chemotherapy. Significant differences were identified in gender, mean tumor diameter, lymphatic invasion, stage, and surgical technique (Table III). The 3-year DFS of 22 patients who received preoperative CRT was 95.5%, whereas that of 94 patients who received neither preoperative CRT nor intensive chemotherapy after surgery was 72.0% (*p*=0.024) (Figure 1). However, there was no significant difference in 5-year DFS between the two groups.

Comparison of DFS between the preoperative CRT and non-CRT groups without intensive adjuvant chemotherapy in stage II rectal cancer. Significant differences were identified

Figure 1. Comparison of disease-free survival (DFS) between the preoperative chemoradiotherapy (CRT) and non-CRT groups without intensive adjuvant chemotherapy.

Figure 2. Comparison of disease-free survival (DFS) between the intensive and oral adjuvant chemotherapy groups.

Table III. Comparison of characteristic between the preoperative chemoradiotherapy (CRT) and non-CRT groups without intensive adjuvant chemotherapy.

Characteristic	CRT (-) (n=94)	CRT (+) (n=22)	p-Value
Mean age (range), years	66.0 (36-80)	63.0 (50-80)	0.160
Gender, n (%)			0.034
Male	59 (63)	19 (86)	
Female	35 (37)	3 (14)	
Mean tumor diameter (range), mm	55.1 (14-108)	35.4 (0-95)	0.003
Pathology, n (%)			0.502
Well-differentiated adenocarcinoma	23 (25)	8 (36)	
Moderately-differentiated adenocarcinoma	64 (68)	13 (59)	
Others	7 (7)	1 (5)	
Lymphatic invasion, n (%)			0.008
Negative	27 (29)	13 (59)	
Positive	67 (71)	9 (41)	
Venous invasion, n (%)			0.092
Negative	33 (35)	12 (55)	
Positive	61 (65)	10 (45)	
Stage, n (%)			0.044
II	47 (50)	16 (73)	
III	47 (50)	6 (27)	
Surgical procedure, n (%)			0.893
Low anterior resection	57 (61)	14 (63)	
Abdominoperineal resection	32 (34)	7 (32)	
Intersphincteric resection	2 (2)	0 (0)	
Hartmann operation	3 (3)	1 (5)	
Surgical technique, n (%)			<0.001
Laparoscopic surgery	46 (43)	19 (86)	
Open surgery	54 (57)	3 (14)	
Recurrence site, n (%)			0.328
Lung	18 (19)	2 (9)	
Liver	8 (9)	1 (5)	
Brain	1 (1)	0 (0)	
Lymph node	2 (2)	0 (0)	
Local	7 (7)	0 (0)

Figure 3. Comparison of disease-free survival (DFS) between the preoperative chemoradiotherapy (CRT) and non-CRT with intensive adjuvant chemotherapy groups.

in gender, mean tumor diameter, lymphatic invasion, venous invasion and surgical techniques. The 3-year DFS of 16 patients who received preoperative CRT was higher than that of 47 patients who received neither preoperative CRT nor intensive chemotherapy after surgery (100% vs. 82.6%), however without statistical significance.

Comparison of DFS between the preoperative CRT and non-CRT groups without intensive adjuvant chemotherapy in stage III rectal cancer. Significant differences were identified in surgical techniques. The 3-year DFS of 6 patients who received preoperative CRT was 83.3%, whereas that of the 47 patients who received neither preoperative CRT nor intensive chemotherapy after surgery was 63.0%, which showed no significant difference.

Table IV. Comparison of characteristic between the intensive and oral chemotherapy after surgery groups in stage III.

Characteristic	Intensive therapy (n=16)	Oral chemotherapy (n=47)	p-Value
Mean age (range), years	60.5 (36-77)	66.2 (40-80)	0.055
Gender, n (%)			0.682
Male	10 (63)	32 (68)	
Female	6 (37)	15 (32)	
Mean tumor diameter (rang), mm	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 (%)			0.011
Laparoscopic surgery	6 (100)	17 (36)	
Open surgery	0 (0)	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)	

Comparison of DFS between the intensive and oral adjuvant chemotherapy groups. Significant differences were identified in surgical techniques and recurrence sites (Table IV). The 3-year DFS of 16 patients who received intensive chemotherapy after surgery without preoperative CRT was 83.7%, whereas that of 47 patients who received oral adjuvant chemotherapy after surgery without preoperative CRT was 63.0% ($p=0.048$) (Figure 2).

Comparison of DFS between the preoperative CRT and non-CRT with postoperative intensive adjuvant chemotherapy groups. Significant differences were identified in mean tumor diameter, stage, and recurrence site (Table V). The 3-year DFS of 22 patients who received preoperative CRT was higher than that of 16 patients who received intensive chemotherapy after surgery without preoperative CRT chemotherapy (95.2% vs. 86.7%), though without statistical significance (Figure 3).

Table V. Comparison of characteristic between the preoperative chemoradiotherapy (CRT) and non-CRT with intensive adjuvant chemotherapy groups.

Characteristic	Intensive therapy (n=16)	CRT (+) (n=22)	p-Value
Mean age (range), years	60.5 (36-77)	63.0 (50-80)	0.420
Gender, n (%)			0.186
Male	10 (63)	19 (86)	
Female	6 (37)	3 (14)	
Mean tumor diameter (range), mm	66.9 (20-100)	35.4 (0-95)	0.001
Pathology, n (%)			0.662
Well differentiated adenocarcinoma	5 (31)	8 (36)	
Moderately differentiated adenocarcinoma	9 (56)	13 (59)	
Others	2 (13)	1 (5)	
Lymphatic invasion, n (%)			0.079
Negative	4 (25)	13 (59)	
Positive	12 (75)	9 (41)	
Venous invasion, n (%)			0.058
Negative	3 (19)	12 (55)	
Positive	13 (81)	10 (45)	
Stage, n (%)			<0.001
II	0 (0)	16 (73)	
III	16 (100)	6 (27)	
Surgical procedure, n (%)			0.306
Low anterior resection	8 (50)	14 (63)	
Abdominoperineal resection	8 (50)	7 (32)	
Intersphincteric resection	0 (0)	0 (0)	
Hartmann operation	0 (0)	1 (5)	
Surgical technique, n (%)			0.832
Laparoscopic surgery	6 (100)	19 (86)	
Open surgery	0 (0)	3 (14)	
Recurrence site, n (%)			0.014
Lung	2 (13)	3 (14)	
Liver	2 (13)	1 (5)	
Brain	1 (6)	0 (0)	
Lymph node	0 (0)	0 (0)	
Local	0 (0)	0 (0)	

Discussion

T4 and/or lateral lymph node metastatic tumors have a high incidence of distant metastasis, even when treated with preoperative CRT, because CRT is considered a localized treatment (19). Accordingly, only patients with lower rectal cancer diagnosed clinical T3 tumors without lateral lymph node metastasis were evaluated in this study.

The preoperative CRT group had a better 3-year DFS compared to the non-CRT group; however, no significant difference was identified in 5-year DFS between the two groups. Preoperative CRT alone has the disadvantage of higher incidence of distant failure at more than 3 years after surgery. In a recent

multicenter randomized phase 3 trial, early T3 rectal cancer did not require CRT, and the same prognosis could be expected with a primary treatment of surgery (20). The tumor regression grade of the primary tumor is associated with oncologic outcome, and there are reports demonstrating that favorable outcomes could be expected in patients who achieved pCR or near-pCR (21-26). In other words, patients who did not achieve pCR or near-pCR after CRT cannot expect favorable outcomes. In patients treated by a contemporary intensive regimen of CRT pCR rates ranged from 20% to 30% (27, 28). In this study, the pCR rate of patients with clinical T3 lower rectal cancer was only 9%.

After the MOSAIC trial in which FOLFOX increased overall survival (29), 12 cycles of FOLFOX became the standard adjuvant regimen for patients with stage III colon cancer. However, it is still quite uncertain whether FOLFOX is the standard adjuvant regimen for patients with stage III rectal cancer. In the current study, the patients who received intensive chemotherapy consisting of oxaliplatin-based regimens after surgery without preoperative CRT had significantly better 3-year DFS compared to patients who received oral adjuvant chemotherapy after surgery without preoperative CRT. Therefore, intensive chemotherapy consisting of oxaliplatin-based regimens appears to be the standard adjuvant regimen for patients with stage III rectal cancer.

It is uncertain whether preoperative CRT or intensive chemotherapy after surgery should be recommended for patients with clinical T3 rectal cancer. In this study, no significant difference was identified in DFS between the preoperative CRT group and the non-CRT with intensive chemotherapy after surgery group. From the view point of patient convenience, intensive chemotherapy after surgery may be a better choice for patients with clinical T3 rectal cancer.

In conclusion, intensive chemotherapy after surgery seems to have an outcome comparable to preoperative CRT in patients with clinical T3 lower rectal cancer without lateral lymph node metastasis; however, a large-scale prospective study is needed to clarify this issue.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

All Authors performed operations, analyzed the data of patients regarding their clinical features, and have been involved in drafting the manuscript. KY had given final approval of the version to be published. All Authors read and approved the final manuscript.

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