ORIGINAL

Long-term outcomes and prognostic factors of preoperative chemoradiotherapy with oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines in patients with locally advanced rectal cancer

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Abstract : Background : The purpose of this study was to determine long-term outcomes and prognostic factors in patients with locally advanced rectal cancer who received preoperative chemoradiotherapy with oral dihydropyrimidine dehydrogenase (DPD)-inhibiting fluoropyrimidines. Methods : Fifty-seven locally advanced rectal cancer patients who underwent preoperative chemoradiotherapy (CRT) with oral DPD-inhibitory fluoropyrimidines from 2006 to 2013 were retrospectively enrolled in this study. Patients with T3–T4 lower rectal cancer were irradiated once daily (2 Gy) with a total dose of 40 Gy, and chemotherapy was administered with tegafur-uracil (300 mg/m²/day) or S-1 (80 mg/m²/day) on radiation days. Results : Five-year overall survival was 77.8% and 5-year disease-free survival was 65.1%. Recurrence was observed in 20 patients (35.1%) and local recurrence in 9 patients (15.8%). Multivariate analysis of prognostic factors for overall survival identified pre-CRT lateral lymph node metastasis and circumferential resection margin as independent prognostic factors, and ypStage as an independent prognostic factor for disease-free survival. Conclusions : Evaluation of lateral lymph node before CRT is useful in predicting prognosis in patients with locally advanced lower rectal cancer treated with preoperative chemoradiotherapy with oral DPD-inhibiting fluoropyrimidines, and surgical planning to ensure a 1-mm circumferential resection margin is important for improving prognosis. J. Med. Invest. 73 : 62-67, February, 2026

Keywords **:** *preoperative CRT, long-term outcome, rectal cancer, S-1, UFT*

INTRODUCTION

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has been shown to significantly reduce local recurrence and has become the standard treatment for locally advanced rectal cancer (1, 2). 5-Fluorouracil (5-FU) is a widely used chemotherapeutic agent for CRT of locally advanced rectal cancer, and many 5-FU derivatives have been developed to enhance its therapeutic efficacy. The oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidines, tegafur-uracil (UFT) and S-1, are oral agents that combine tegafur, a prodrug of 5-FU, with a DPD inhibitor. UFT and S-1 have the clinical advantages of enhanced antitumor efficacy by increasing intratumoral 5-FU concentrations and the convenience of oral administration. The combination of UFT and radiotherapy has been shown to be well tolerated in the preoperative treatment of rectal cancer (3-5), while gimelacil, a component of S-1, is a potent radiosensitizer and has a 180-fold higher DPD inhibitory effect compared with uracil (6).

We previously conducted a multicenter phase II study to evaluate the efficacy and toxicity of CRT with UFT or S-1 in patients with locally advanced rectal cancer. The pathologic response rate was 57% in the S-1 group and 45% in the UFT group. The pathologic complete response rate was 7% in the S-1 group and 4% in the UFT group. The incidence of grade 3 diarrhea was reported in the UFT group (0%) and the S-1 group (7%), indicating that CRT using UFT or S-1 is effective and feasible for patients with locally advanced rectal cancer (7). In the present study, we analyzed long-term outcomes, prognostic factors for overall survival (OS) and disease-free survival (DFS), and local recurrence factors in patients who received UFT- and S-1-based preoperative CRT at our hospital.

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MATERIALS AND METHODS

The study was approved by the Tokushima University Hospital ethics committee (approval number 3215). All study participants provided written informed consent.

Patients and study design

Fifty-seven patients with locally advanced rectal cancer who underwent preoperative CRT with oral DPD-inhibitory fluoropyrimidines at our hospital from 2006 to 2013 were retrospectively enrolled in this study. For patients with T3–T4 low rectal cancer, chemoradiotherapy with UFT or S-1 was provided after securing adequate informed consent. Irradiation was performed once (2 Gy) daily to a total dose of 40 Gy. Concomitant chemotherapy with UFT (300 mg/m²/day) or S-1 (80 mg/m²/day) was administered on days of radiation administration. UFT and S-1 were simultaneously given with radiotherapy on 5 weekdays, followed by a 2-day rest on weekends.

TME was performed 6–8 weeks after the completion of radiotherapy. A lateral lymph node (LLN) with a short axis of ≥7 mm on magnetic resonance imaging was defined as positive for metastasis based on previous reports (8). Patients diagnosed with positive LLN metastasis underwent selective lateral lymph

node dissection (LLND) on the positive side. The final pathologic features were restaged according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (9) at the time of data review. Freshly obtained resected specimens were cut longitudinally along the anterior wall of the rectum, mounted on a cork board, and fixed in formalin. The specimen was then sliced transversely at regular intervals (usually 3-5 mm thick). The CRM was defined as the shortest distance between the tumor margin and the radial edge of the resected tissue and was assessed by a pathologist. A positive circumferential resection margin (CRM) was defined as tumor within 1 mm of the transected margin (10, 11). Histological criteria for the assessment of response to chemoradiotherapy was classified from grade 0 to 3 (9). To summarize briefly, Grade 0 : No tumor cell necrosis or degeneration is observed. Grade 1a : Tumor cell necrosis or degeneration is present in less than one-third of the entire lesion. Grade 1b : Tumor cell necrosis, degeneration, and/or lytic change is present in more than one-third but less than two-thirds of the entire lesion. Grade 2 : Prominent tumor cell necrosis, degeneration, lytic change, and/or disappearance is present in more than two-thirds of the entire lesion, but viable tumor cells remain. Grade 3 : No viable tumor cells are observed.

Statistical analysis

Continuous data are presented as the median and range and categorical data as the number. Kaplan–Meier survival analysis was performed for OS and DFS rates. Univariate and multivariate logistic regression analyses were performed to evaluate the prognostic factors after neoadjuvant CRT for locally advanced rectal cancer. All statistical analyses were performed using JMP Pro software (version 17 ; SAS Institute Inc., Cary, NC, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of patients receiving preoperative single-drug regimen-based chemoradiotherapy. There were 41 men and 16 women with a median age of 69 years. Prior to CRT, 15 patients had clinical stage II disease and 42 had clinical stage III disease. The chemotherapeutic drugs administered concurrently with preoperative radiotherapy were S-1 in 42 patients (73.7%) and uracil-tegafur in 15 patients (26.3%). All patients had clinical T3 or T4 disease before CRT, and 73.7% had clinical lymph node metastases. However, after CRT, the proportion of patients with pathological T3 or T4 lesions decreased to 57.9%, and the proportion of patients with pathological lymph node metastases decreased to 28.1% (Table 2). Pathological complete response (pCR) was observed in three patients (5.6%). The number of patients with grade 2 or 3 responses was 15, providing a pathological response rate of 26.3%. LLND was performed in six patients, and metastasis was found in five patients.

Table 1. Characteristics of patients receiving preoperative single-drug regimen-based chemoradiotherapy

Variable	(n = 57)
Age	69 (38–86)
sex (M/F)	41/16
BMI	24.0 (16.0–33.4)
Concurrent chemotherapy (S-1/uracil-tegafur)	42/15
Pre-CRT CEA	2.8 (0.3–182.0)
Pre-CRT CA19-9	13 (1–634)
Pre-CRT Stage (2/3)	15/42
Pre-CRT T stage (3/4)	55/2
Pre-CRT LLN metastasis (+/–)	7/50
Post-CRT CEA	1.5 (0.2–9.9)
Post-CRT CA19-9	11 (1–222)
Post-CRT Stage (1/2/3)	7/26/24
Post-CRT T stage (1/2/3/4)	2/6/49/0
Post-CRT LLN metastasis (+/–)	5/52
AV (cm)	4 (1–8)
Surgical approach (open/lap)	5/52
Surgical procedure (LAR/ISR/APR)	25/8/24
LLND (+/–)	6/51
Operative time (min)	300 (172–724)
Intraoperative bleeding (ml)	125 (1–1560)
Anastomotic leakage (+/–)*	4/29
Hospital stay (days)	22 (9–78)
Adjuvant therapy (+/–)	12/45

BMI, body mass index ; CEA, carcinoembryonic antigen ; CA19-9, carbohydrate antigen 19-9 ; LLN, lateral lymph node ; AV, anal verge ; LAR, low anterior resection ; ISR, internal sphincter resection ; APR, abdominoperineal resection ; LLND, lateral lymph node dissection. *Excludes APR cases.

Survival analysis and prognostic factors

The median follow-up was 71 months (range, 1–195 months). Five-year OS was 77.8%, and 5-year DFS was 65.1% (Fig.1). Recurrence was found in 20 patients (35.1%). The initial site of recurrence was locoregional in six patients (10.5%), liver in five patients (8.8%) and lung in nine patients (15.8%). Local recurrence was found in nine patients (15.8%) during the observation period. Among the six cases undergoing LLND, local recurrence occurred in only one case (16.7%), and recurrence was observed within the lateral region. However, distant metastasis was detected in two cases (lung : one case, lung and liver : one case). In contrast, among the 51 cases where LLN metastasis was determined to be negative, local recurrence was observed in eight cases (15.7%).

Table 3 shows the results of univariate and multivariate analyses of prognostic factors for OS. Pre-CRT LLN metastasis, ypStage, and circumferential resection margin (CRM) were extracted in the univariate analysis, and pre-CRT LLN metastasis and CRM were identified as independent prognostic factors in the multivariate analysis (Fig.2). In addition, Table 4 shows the results of univariate and multivariate analyses of prognostic factors for DFS. ypStage, ly, CRM, and therapeutic effect were extracted in the univariate analysis, and ypStage was identified as an independent prognostic factor in the multivariate analysis Fig.2.

Table 2. Pathological findings of patients receiving preoperative single-drug regimen-based chemoradiotherapy

Variable	(n = 57)
ypStage (CR/1/2/3/4)	3/20/18/15/1
Maximum tumor diameter (mm)	30 (0–80)
Differentiation (tub1/tub2/por)	22/34/1
pT (CR/1/2/3/4)	3/5/16/32/1
ly (0/1/2/3)	45/11/1/0
v (0/1/2/3)	27/16/11/4
pN (+/–)	16/41
pLLN mets (+/–)*	5/0
Harvested LN (total)	7 (1–23)
Harvested LN (LLN)*	5 (1–11)
CRM (≤ 1 mm/ > 1 mm)	7/50
Therapeutic effect (grade 0/1/2/3)	1/41/12/3

CR, complete response ; LLN, lateral lymph node ; LN, lymph node ; CRM, circumferential resection margin

DISCUSSION

In this study, we identified pre-CRT LLN metastasis and CRM as independent prognostic factors for OS and ypStage as an independent prognostic factor for DFS in patients treated with preoperative chemoradiotherapy with oral DPD-inhibiting fluoropyrimidines.

Various prognostic factors have been reported for patients with lower rectal cancer undergoing 5-fluorouracil-based preoperative chemoradiotherapy. Guillem *et al*. (12) reported in a multivariate analysis that pathologic response >95%, lymphovascular and/or perineural invasion, and positive lymph nodes were significantly associated with OS and RFS. Furthermore, similar to our results, it has been reported that post-treatment pathologic stage is more strongly associated with DFS than pre-CRT clinical stage in patients with rectal cancer who received 5-fluorouracil-based preoperative CRT (13, 14). In addition, a CRM smaller than 1 mm has been shown to be an independent predictor of risk of local recurrence and survival (10, 11), suggesting that the same is true for radical surgery after CRT.

Several short-term outcomes of preoperative chemoradiotherapy with oral DPD-inhibiting fluoropyrimidines have been reported. In a study using UFT, Vestermark *et al*. (4) treated patients with UFT (300 mg/m^2/day) and l-LV (22.5 mg) 5 days a week for 6 weeks with concurrent high-dose (60 Gy) pelvic radiation therapy, including boost, and reported a pCR rate of 13%. Fernández-Martos *et al*. (15) treated patients with UFT (400 mg/m^2/day, 5 days/week for 5 weeks) and conventional dose (45 Gy) pelvic radiation therapy and reported a pCR rate of 9%. In a report using S-1, patients were treated with 80 mg/m^2/day S-1 and 45 Gy to 50.4 Gy radiation therapy and reported pCR rates of 11% to 28.1% (16-18). The present study showed a lower pCR rate (5.6%) than these reports, which may be due to the low volume of UFT (300 mg/m^2/day) and low radiation dose (40 Gy).

This study suggested that even in cases with positive LLN metastasis, performing LLND after preoperative CRT resulted in a local recurrence rate comparable to that of cases with negative LLN metastasis, indicating that LLND may contribute to suppressing local recurrence. Ogura *et al*. reported that for LLNs with a short axis ≥7 mm on MRI, the 5-year local recurrence rate was 19.5% in the group receiving preoperative CRT alone, compared to 5.7% in the group receiving LLND after preoperative CRT, indicating that LLND contributes to the suppression of local recurrence (19).

There are several limitations of this study. First, it was a single-center study and the number of cases was small. Second, because this was a retrospective study, the indications for postoperative adjuvant chemotherapy were not determined, which

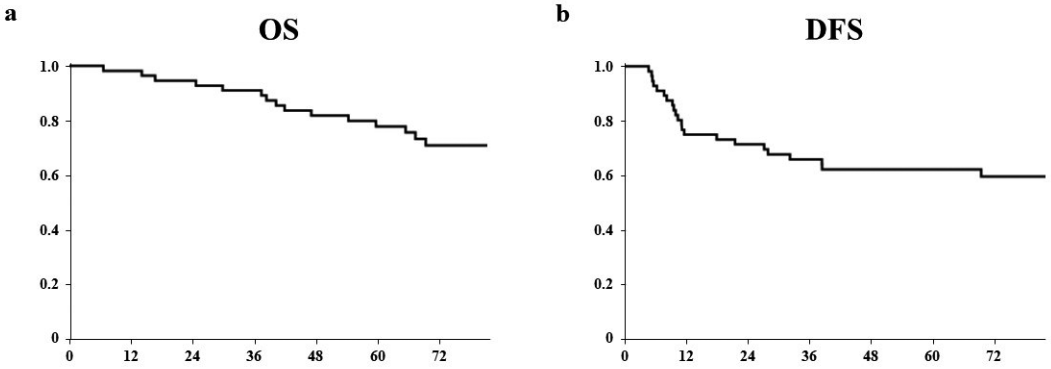

Fig 1.

Table 3. Univariate and multivariate Cox proportional hazard regression analyses in overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (< 65/≥ 65)	1.36	0.49–3.75	0.56			
Sex (M/F)	0.74	0.25–2.16	0.64			
BMI (< 25/≥ 25)	1.85	0.63–5.45	0.26			
Pre-CRT CEA (< 5/≥ 5)	0.90	0.30–2.64	0.85			
Pre- CRT CA19-9 (< 37/≥ 37)	0.61	0.20–1.93	0.41			
Pre-CRT Stage (2/3)	0.19	0.03–1.48	0.11			
Pre-CRT T Stage (3/4)	0.46	0.06–3.48	0.45			
Pre-CRT LLN metastasis (+/–)	5.57	1.87–16.60	< 0.01	7.62	1.55–37.4	0.01
Post-CRT CEA (< 5/≥ 5)	0.37	0.10–1.32	0.13			
Post-CRT CA19-9 (< 37/≥ 37)	0.70	0.15–3.10	0.64			
AV (cm) (< 3/≥ 3)	1.45	0.51–4.06	0.49			
Surgical approach (open/lap)	2.02	0.45–9.00	0.36			
Surgical procedure (LAR, ISR/APR)	0.76	0.27–2.09	0.59			
Operative time (min) (< 300/≥ 300)	0.96	0.34–2.65	0.94			
Intraoperative bleeding (ml) (< 100/≥ 100)	0.50	0.17–1.47	0.21			
Anastomotic leakage (+/–)*	1.03	0.14–7.87	0.98			
Hospital stay (day) (< 22/≥ 22)	0.51	0.18–1.51	0.22			
ypStage (≤ 2/≥ 3)	0.24	0.08–0.66	< 0.01	0.78	0.20–3.02	0.72
Maximum tumor diameter (mm) (< 40/≥ 40)	0.36	0.13–1.04	0.06			
pT (≤ 2/≥ 3)	0.41	0.13–1.29	0.13			
ly (0/1, 2, 3)	0.47	0.16–1.39	0.17			
v (0/1, 2, 3)	0.72	0.26–2.02	0.53			
Harvested LN (total) (< 7/≥ 7)	0.82	0.29–2.33	0.72			
CRM (≤ 1 mm/> 1 mm)	6.62	2.19–20.01	< 0.01	10.04	2.68–37.61	< 0.01
Therapeutic effect (grade 0, 1/2, 3)	5.64	0.74–42.99	0.09			

CI, confidence interval ; BMI, body mass index ; CRT, chemoradiotherapy ; CEA, carcinoembryonic antigen ; CA19-9, carbohydrate antigen 19-9 ; LLN, lateral lymph node ; AV, anal verge ; LAR, low anterior resection ; ISR, internal sphincter resection ; APR, abdominoperineal resection ; CRM, circumferential resection margin ; HR, hazard ratio. *Excludes APR cases.

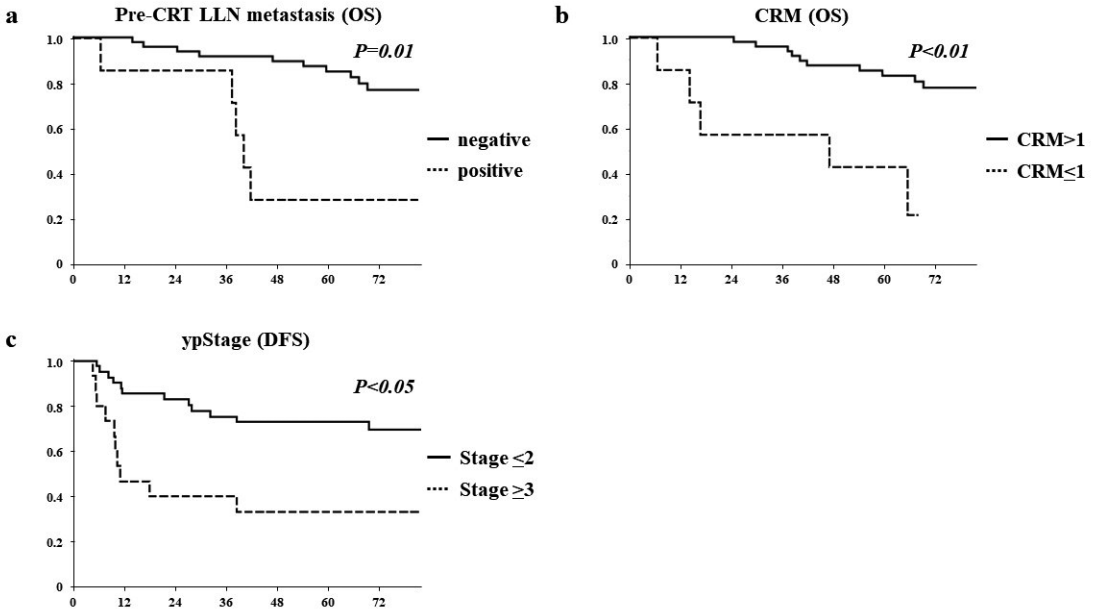

Fig 2.

Table 4. Univariate and multivariate Cox proportional hazard regression analyses in disease-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (< 65/≥ 65)	1.08	0.46–2.52	0.87			
Sex (M/F)	0.61	0.26–1.46	0.27			
BMI (< 25/≥ 25)	1.49	0.62–3.57	0.37			
Pre-CRT CEA (< 5/≥ 5)	1.14	0.45–2.92	0.78			
Pre- CRT CA19-9 (< 37/≥ 37)	0.53	0.21–1.36	0.19			
Pre-CRT Stage (2/3)	0.76	0.28–2.07	0.60			
Pre-CRT T Stage (3/4)	0.98	0.13–7.27	0.98			
Pre-CRT LLN metastasis (+/–)	2.47	0.91–6.72	0.08			
Post-CRT CEA (< 5/≥ 5)	0.63	0.18–2.12	0.45			
Post-CRT CA19-9 (< 37/≥ 37)	0.74	0.22–2.50	0.63			
AV (cm) (< 3/≥ 3)	2.01	0.87–4.66	0.10			
Surgical approach (open/lap)	1.08	0.25–4.65	0.91			
Surgical procedure (LAR, ISR/APR)	0.67	0.29–1.54	0.34			
Operative time (min) (< 300/≥ 300)	1.71	0.73–3.99	0.22			
Intraoperative bleeding (ml) (< 100/≥ 100)	0.73	0.31–1.72	0.48			
Anastomotic leakage (+/–)*	0.51	0.07–3.80	0.51			
Hospital stay (days) (< 22/≥ 22)	0.81	0.35–1.90	0.63			
ypStage (≤ 2/≥ 3)	0.29	0.12–0.67	< 0.01	0.41	0.16–0.99	< 0.05
Maximum tumor diameter (mm) (< 40/≥ 40)	0.49	0.20–1.18	0.11			
pT (≤ 2/≥ 3)	0.60	0.24–1.48	0.27			
ly (0/1, 2, 3)	0.25	0.10–0.60	< 0.01	0.44	0.17–1.13	0.09
v (0/1, 2, 3)	0.77	0.33–1.81	0.56			
Harvested LN (total) (< 7/≥ 7)	0.60	0.25–1.44	0.26			
CRM (≤ 1 mm/> 1 mm)	3.56	1.29–9.80	0.01	2.12	0.73–6.23	0.16
Therapeutic effect (grade 0, 1/2, 3)	4.46	1.04–19.10	0.04	3.81	0.88–16.49	0.17

CI, confidence interval ; BMI, body mass index ; CRT, chemoradiotherapy ; CEA, carcinoembryonic antigen ; CA19-9, carbohydrate antigen 19-9 ; LLN, lateral lymph node ; AV, anal verge ; LAR, low anterior resection ; ISR, internal sphincter resection ; APR, abdominoperineal resection ; CRM, circumferential resection margin ; HR, hazard ratio. *Excludes APR case.

may have affected the prognosis. Third, although both S-1 and UFT are oral administered DPD-inhibitory fluoropyrimidines, their differing pharmacological properties may have influenced the results.

In conclusion, evaluation of LLN before CRT is important to predict prognosis in patients with locally advanced lower rectal cancer treated with preoperative chemoradiotherapy consisting of oral DPD-inhibiting fluoropyrimidines, and a surgical plan that ensures a CRM of at least 1 mm is important to improve OS. In addition, it was suggested that postoperative adjuvant chemotherapy selection based on pathologic stage may be important to improve DFS.

DISCLOSURES

Takuya Tokunaga, Hideya Kashihara, Toshihiro Nakao, Toshiaki Yoshimoto, Masaaki Nishi, Chie Takasu, Yuma Wada and Yuji Morine declare that they have no conflict of interest.

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