

ORIGINAL RESEARCH ARTICLE

A phase I study of oral UFT/leucovorin and irinotecan, plus radiation for locally recurrent rectal cancer

Masataka Ikeda¹⁾, Mitsugu Sekimoto¹⁾, Yosuke Fukunaga²⁾, Koji Konishi³⁾, Yushi Fujiwara⁴⁾, Tsunekazu Mizushima⁵⁾, Ichiro Takemasa⁵⁾, Hirofumi Yamamoto⁵⁾, Yuichiro Doki⁵⁾ and Masaki Mori⁵⁾

1) Department of Surgery, Osaka National Hospital, Osaka, Japan

2) Department of Gastroenterological Surgery, Cancer Institute Hospital, Tokyo, Japan

3) Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

4) Department of Gastroenterological Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

5) Department of Surgery, Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Japan

Abstract:

Objectives: The aim of this phase I study is to identify the maximum tolerated dose (MTD) and recommended dose (RD) of CPT-11 in combination with UFT/LV and radiation in patients with locally recurrent rectal cancer. **Methods:** Patients with histologically proven rectal cancer with local recurrence were eligible for this study. Escalating doses of CPT-11 (30-60 mg/m²) were administered on days 3, 10, 24, and 31. UFT (300 mg/m²) and LV (75 mg/body) were given on days 1-5, 8-12, 22-26, and 29-33. Radiotherapy doses consisted of 50 Gy in daily fractions of 2.0 Gy each, 5 times per week, for total 5 weeks. **Results:** We recruited 27 patients, and the MTD of CPT-11 was 60 mg/m² due to the occurrence of dose-limiting toxicity of grade 3 diarrhea. Major grade 3 adverse events were neutropenia (5/27; 18.5%) and diarrhea (6/27; 22.2%). No grade 4 adverse event was observed throughout this treatment. **Conclusions:** The combined chemoradiotherapy with oral UFT/LV plus CPT-11 is feasible and promising. The recommended dose for further phase II trials is determined to be 50 mg/m² of CPT-11.

Keywords:

locally recurrent rectal cancer, chemoradiation, CPT-11, UFT/LV, phase I study

J Anus Rectum Colon 2017; 1(2): 50-55

Introduction

Due to recent advances in rectal cancer treatment, preoperative chemoradiotherapy (CRT) is widely used for the treatment of locally advanced rectal cancer. Three randomized trials comparing preoperative CRT and chemotherapy showed that preoperative CRT had better improvement in the local recurrence rate than chemotherapy¹⁻³⁾. However, local recurrence (LR) remains a significant problem in rectal cancer treatment. The reported incidence of LR ranges between 5% and 30% after curative resection⁴⁻⁷⁾. The standard therapy for locally recurrent cancer treatment remains to be established.

UFT is one of the oral fluoropyrimidines that combines uracil and tegafur in a fixed molar ratio of 4:1. Tegafur is a

prodrug of 5-FU that acts as an effector. Uracil is a competitive inhibitor of the enzyme dihydropyrimidine dehydrogenase. Results from three large randomized studies have shown that UFT and leucovorin (LV) had similar efficacy with less toxicity than conventional 5-FU/LV in patients with metastatic^{8,9)} and adjuvant¹⁰⁾ settings. Combination chemotherapy of UFT/LV plus irinotecan (CPT-11) seems to be an attractive option in the treatment of metastatic colorectal cancer, because of their ease of administration. Some phase II studies have shown that the UFT/LV/CPT-11 combination chemotherapy is effective and well tolerated for metastatic colorectal cancer¹¹⁻¹⁵⁾. Giralt *et al.* reported a phase II trial of preoperative CRT with UFT/LV in patients with advanced rectal cancer¹⁶⁾. Complete resection was achieved in 91% of the patients, and grade 1 tumor regression was obtained in

Table 1. Dose Escalation Strategy.

	CPT-11 (mg/m ²)	UFT (mg/m ² tid)	LV (mg/m ² tid)
Level 1	30	300	75
Level 2	40	300	75
Level 3	50	300	75
Level 4	60	300	75
Level 5	70	300	75

24% of the patients in this trial. However, there are little reports of investigating UFT/LV/CPT-11 combined with radiotherapy.

The treatment for locally recurrent rectal cancer has not been well established. The treatment option depends on the previous treatment. Radiation, chemotherapy, surgery or a combination of these modalities has been employed. Radiotherapy is used to improve local control and respectability. We have previously reported the preliminary results of phase I trial of UFT/LV/CPT-11 with radiotherapy for locally recurrent rectal cancer¹⁷). Due to diarrhea in this setting, it was concluded that a modification of the treatment schedule was needed. In this treatment, CPT-11 was administered on days 1, 8, 15, and 22. UFT/LV was given on days 3 to 7, 10 to 14. As grade 3 diarrhea occurred around the 3rd week, the treatment was modified to put chemotherapy-rest during the third week, and oral UFT/LV were to be administered on the same day of radiation to make complete treatment-free days.

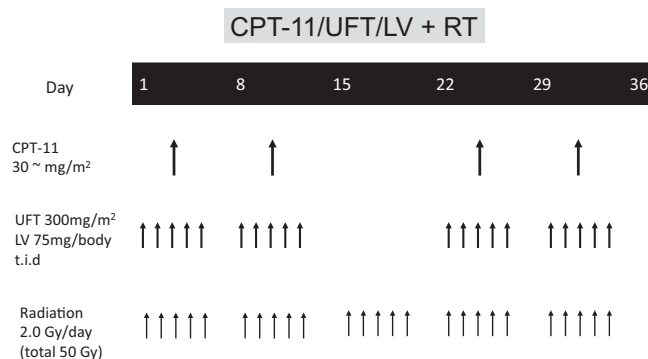
Based on these results, we set out in the phase I trial to investigate the combination of UFT/LV/CPT-11 with radiotherapy in patients with recurrent rectal cancer in a modified treatment schedule. The present phase I study was designed to evaluate the maximum tolerated dose (MTD) and recommended dose (RD) of CPT-11 in combination with UFT/LV and radiation.

Methods

The study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Osaka University Hospital. Written informed consent was obtained from all patients before study participation.

Eligibility criteria

Patients with histologically proven rectal cancer with LR were eligible for the study. Further eligibility requirements included: at least a four week rest from the prior treatment; age 20-75 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; an expected survival of at least 3 months; adequate bone marrow, renal, cardiac and hepatic function (leukocyte count 4000-12000/mm³, a neutrophil count \geq 2000/mm³, a hemoglobin count \geq 9.0 g/dL, serum aspartate aminotransferase and alanine aminotransferase levels \leq 100 IU/L, a total bilirubin concentration

**Figure 1.** Schema of the treatment schedule.

\leq 1.5 mg/dL, normal electrocardiographic findings), and the ability of oral intake. Resectability was not considered in this study eligibilities.

Treatment

RT was delivered with a linear accelerator with using 10-MV photons with an anterior-posterior opposing field or three-field technique consisting of a posterior and two lateral fields. For three-dimensional treatment planning purposes, all patients had a computed tomographic (CT) scan in the treatment position. A planned irradiation was given in daily fractions of 2.0 Gy, 5 days a week, for 5 consecutive weeks, resulting total dose of 50 Gy. The clinical target volume (CTV) included the recurrent tumor with 1-1.5 cm margin, sacrum, and the presacral space. The upper border of the CTV was at the L5-S1 interspace. The lower field border was 3 cm below the macroscopic tumor. The planning target volume (PTV) margin was 5 mm from the CTV. Unless a patient had one of the following adverse events: leukopenia \geq grade 3, neutropenia \geq grade 3, thrombocytopenia \geq grade 3, diarrhea \geq grade 2, the irradiation was not interrupted. In these occurrences, RT was withheld until adverse events resolved¹⁷).

UFT/LV was given on days 1-5, 8-12, 22-26, and 29-33. The daily dose of UFT was 300 mg/m²/day and that of LV was 75 mg/body/day, which were given orally three times per day with 8 hours interval in each administration. CPT-11 was administered as an intravenous infusion over 90 minute on days 3, 10, 24, and 31. The dose of CPT-11 was tested ranging from 30 to 60 mg/m² (Table 1 and Figure 1).

Dose-limiting toxicity

Adverse events were classified according to the Common Toxicity Criteria of the National Cancer Institute, version 2. The dose-limiting toxicity (DLT) was defined as any of the following experienced during the 5 week treatment period; grade 4 hematological toxicity; grade 3 or more thrombocytopenia; grade 3 or more non-hematological toxicity; radiotherapy interruption over 1 week; inability of CPT-11 administration over 2 times; and less than 14 days of UFT/LV administration as planned.

The dose of CPT-11 was escalated stepwise (Table 1). At

Table 2. Patients and Disease Characteristics at Base Line (n=27).

Characteristics	No. of patients (%)
Age	
Median	63
Range	36-73
Sex	
Female	22 (81.5)
Male	5 (18.5)
Performance status	
0	26 (96.3)
1	1 (3.7)
Primary surgery	
AR/LAR	20 (74.1)
APR	7 (25.9)
Metastatic lesion	
Local recurrence	23 (85.2)
Distant metastasis	4 (14.8)
CEA (ng/mL)	
Median	12
Range	1-1022

AR: anterior resection, LAR: low anterior resection, APR: abdominoperineal resection

least three patients were accrued at each dose level. The MTD was defined as the dose level that caused DLT in at least in 3 out of 6 patients. Dose escalation was permitted if no DLT was observed in the treatment. If DLT occurred in 1 or 2 of the first patients, 3 additional patients were accrued at the same dose. If 1 or 2 out of 6 patients had DLT, the dose was increased to the next level. In order to evaluate the efficacy and safety of the RD, an additional 5 more patients were recruited on the RD level.

Evaluation

The primary endpoint of the study was an estimation of the MTD and RD. The secondary endpoints were pathological responses, R0 resection rates, overall survival, and carcinoembryonic antigen (CEA) levels. Histological changes after the treatment were evaluated for the patients who underwent resection according to the General Rules of Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus¹⁸⁾. Shortly, Grade 0 means no histological change. Grade Ia is defined as necrosis or the disappearance of the tumor present in less than 1/3 of the whole lesion, and grade Ib is defined as the histological change between 1/3 and 2/3. Grade 2 indicates a moderate change, that is, necrosis or the disappearance of the tumor present in more than 2/3 of the whole lesion, but viable tumor cells still remain. Grade 3 means a complete response. Survival curves were estimated by the Kaplan-Meier method.

Results

A total of 27 patients of locally recurrent rectal cancer were accrued into this study from October 2004 through De-

Table 3. Dose-limiting Toxicity

Patient-No.	Level	No. of patients with DLT	Adverse events (grade)
2-2	2	1/6	Diarrhea (3)
3-1	3	1/6	Diarrhea (3)
4-3	4	3/6	Diarrhea (3)
4-4	4		Diarrhea (3)
4-5	4		Diarrhea (3)

cember 2007. Their clinical characteristics are presented in Table 2. Their median age was 63 years (range 36-73); 22 men and 5 women patients. An anterior resection or low anterior resection was performed in 20 patients, and an abdominoperineal resection was done in seven patients. 23 patients had only LR and four patients had local and metastatic recurrence. One patient did not have LR by the final histological diagnosis after resection.

All patients were evaluable for toxicity. The adverse events observed in each level were shown in Table 3 and 4. Three patients were treated at level 1 (30 mg/m² of irinotecan) with no DLT. Six patients were treated at level 2 (40 mg/m² of irinotecan) in which 1 patient (second patient) had grade 3 diarrhea. At level 3 (50 mg/m² of irinotecan), two patients stopped treatment due to the grade 2 diarrhea, and one patient (the first patient) had grade 3 diarrhea. Two cases of grade 3 leukopenia and one case of grade 3 neutropenia were observed at this level. Of the six patients treated at level 4 (60 mg/m² of irinotecan), three had grade 3 diarrhea (third to fifth patients). No grade 4 adverse events occurred in all levels. Grade 3 diarrhea occurred only in patients with a low anterior resection. Therefore, MTD of CPT-11 was determined to be 60 mg/m² due to the occurrence of dose-limiting diarrhea. The dose of 50 mg/m² irinotecan was considered to be the RD. The median total doses of radiation were 48 Gy at level 1, 50 Gy at level 2, 50 Gy at level 3, and 50 Gy at level 4.

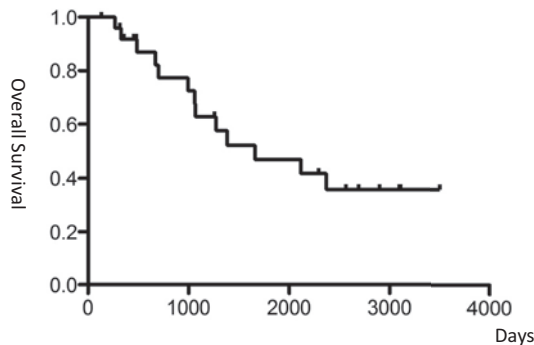
Of the 27 patients who received UFT/LV/CPT-11 and radiotherapy, 19 patients underwent surgery after this treatment. Pathological response was evaluated in these 18 of 19 patients (one patient did not have LR). The tumor regression grade, according to Japanese pathological criteria¹⁸⁾, was as follows: 0 was found in 1 patient (6%), grade Ia was observed in eight patients (44%), and grade 2 in nine patients (50%) (Table 5). Overall survival is shown in Figure 2. The 5-year overall survival rate of 26 patients with LR was 47.1%, and the median overall survival time was 1661 days. The median CEA level was 12 (ng/ml) before the treatment. There was a statistically significant decrease in the median CEA level, which shifted down from 12 to 3 (ng/ml) by the treatment (Figure 3).

Discussion

We set out this phase I study of UFT/LV/CPT-11 in combination with radiotherapy to evaluate the MTD and RD of

Table 4. Frequency of Adverse Events in Each Level.

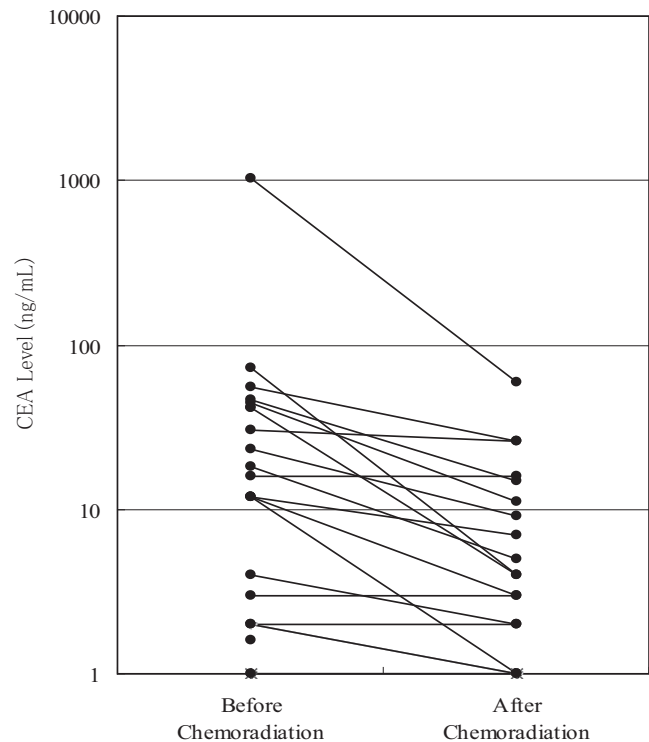
	Level 1 (n=3)		Level 2 (n=6)		Level 3 (n=12)		Level 4 (n=6)	
	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3
Hematological								
Leukopenia	2	0	3	0	8	2	4	3
Neutropenia	1	0	1	0	6	1	4	1
Thrombocytopenia	0	0	0	0	2	0	0	0
Anemia	3	0	6	0	12	0	5	0
Non-hematological								
Anorexia	3	0	1	0	9	0	5	0
Nausea	3	0	3	0	7	0	5	0
Vomiting	2	0	0	0	5	0	3	0
Diarrhea	3	0	4	1	10	1	5	3
Abdominal pain	2	0	1	0	9	0	4	0
AST/ALT elevation	0	0	0	0	2	0	2	0
Total bilirubin	0	0	0	0	2	0	0	0
Creatinine	2	0	0	0	0	0	1	0

**Figure 2.** Overall survival curve.

irinotecan in patients with locally recurrent rectal cancer. The MTD were determined to be 60 mg/m² of irinotecan on the basis of diarrhea in three out of six patients enrolled at level 4. Twelve patients registered at the RD (CPT-11 50 mg/m²) and safely completed the 5-week treatment.

From the reports of UFT/LV plus radiotherapy, diarrhea was the most frequent of the adverse events, and the incidence resulted in 10-20%^{16,19-22)} of the patients. The occurrence of diarrhea in these patients, which commonly appeared in 2-4 weeks, seemed to be associated with the treatment program. In fact, most of the diarrheas were observed on week three in our previous reports. Grade 3 diarrheas occurred in four out of six patients, although CPT-11 was administered at the lower dose (30 mg/m²) than the present study. The notable difference between these two studies was the existence of the chemotherapy free period on week three; an appropriate chemotherapy free period is indicated to be important for the management of diarrhea in concomitant CRT.

Adhesion is observed in a recurrent tumor more often than the primary tumor, which is different from neo-adjuvant treatment for primary rectal cancer. Particularly,

**Figure 3.** Serum CEA levels before and after chemoradiation.

when the small intestines in the pelvic area are fixed or invaded by the LR, it is susceptible to CRT, because of an adjacent inflammation by the tumor. Cautious treatment is required to prevent perforation or bowel obstruction due to radiation enteritis, especially in non-operable cases. In addition, adhesion makes the tumor resection more complicated in operable cases.

In the SAMURAI-1 multicenter phase I trial using S-1, irinotecan plus radiation for primary advanced rectal cancer, the RD for irinotecan was 60 mg/m², which is a higher dose than our study. Moreover, the incidence of diarrhea as DLT

Table 5.

Response (n=18)	N (%)
Grade 0	1 (6%)
Grade Ia	8 (44%)
Grade Ib	0 (0%)
Grade 2	9 (50%)
Grade 3	0 (0%)

Histological changes were determined according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus (18).

Grade 0: No change. Neither necrosis nor cellular or structural change can be seen throughout the lesion.

Grade Ia: Necrosis or the disappearance of the tumor is present in less than 1/3 of the whole lesion, or only cellular or structural changes are visible in variable amounts.

Grade Ib: Necrosis or the disappearance of the tumor is present in less than 2/3 of the whole lesion.

Grade 2: A moderate change. Necrosis or the disappearance of the tumor is present in more than 2/3 of the whole lesion, but viable tumor cells still remain.

Grade 3: A severe change. The whole lesion falls into necrosis and/or is replaced by fibrosis, with or without granulomatous changes. No viable tumor cells are observed.

was in two patients with irinotecan 60 mg/m², and 1 patient with 90 mg/m²²³. Other DLTs, such as hematological adverse events, were much more common in the SAMURAI-1 study. In contrast, diarrhea was the only cause for DLT in our study, suggesting that UFT/LV and the post-operative status may play a pivotal role on adverse events. Another phase I study employing capecitabine, irinotecan (50 mg/m²), and radiation demonstrated that diarrhea was not observed in the lower dose (500 mg/m² bid), however it was the most common DLT (3 of 7 patients) in the higher dose of capecitabine (625 mg/m² bid)²⁴. As S-1 includes oteracil potassium, that prevents gastrointestinal toxicity caused by 5-FU, the incidence of diarrhea might be lower in the SAMURAI-1 study. Oxaliplatin was not approved at the beginning of this study, and recently, phase I trials of S-1, oxaliplatin, and radiation have been reported^{25,26}. Grade 3 diarrhea was not observed in both trials, strongly suggesting that using these drugs may prevent severe diarrhea caused by CRT. We did not perform a phase II study of this regimen, because we had recruited six more patients in level 3; we would like to prevent diarrhea before operations as much as possible. However, this regimen might be very useful in patients resistant to oxaliplatin-based chemotherapy.

UFT/LV plus radiotherapy shows a 40-50% down staging rate and almost a 10% pathological complete response rate from the results of neo-adjuvant CRT in locally advanced rectal cancer patients^{16,19-21}. Although the efficacy was not a primary endpoint in this phase I study, our UFT/LV/CPT-11 plus radiotherapy program seems to be promising as 50% of the patients showed a pathological response in more than 2/3 of the whole tumor lesion.

Four out of 27 patients had distant metastases in our

study. Considering an effect of systemic chemotherapy is also required for locally recurrent rectal cancer. There are several reports investigating the systemic effects of UFT/LV/CPT-11 in combination with chemotherapy for metastatic colorectal cancer¹¹⁻¹⁵. According to these results, the response rate was almost 50%, and the progression-free survival was seven months. Furthermore, the present results, with 16 out of 24 patients undergoing surgery after CRT, are very encouraging. Our UFT/LV/CPT-11 plus radiotherapy program is expected to control locally recurrent disease with radiotherapy and treat local and metastatic disease with UFT/LV/CPT-11 systemic chemotherapy. Further studies are needed in a larger population to confirm the overall effect of CRT for locally recurrent rectal cancer.

The limitations of this study are that this is a phase I study that needs to be confirmed by a phase II study, the efficacy on distant metastasis of patients with locally recurrent rectal cancer was not evaluated, and it is difficult to apply this regimen on patients with primary rectal cancer.

In summary, UFT/LV/CPT-11 combined with radiotherapy is safe and tolerable for locally recurrent rectal cancer. The recommended dose of CPT-11 is determined to be 50 mg/m².

Conflicts of Interest

MM received a research funding from Taiho Pharmaceutical Co. Ltd. Other authors declare that there are no conflicts of interest.

References

1. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006 Sep; 355(11): 1114-23.
2. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg.* 2006 Oct; 93(10): 1215-23.
3. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois E, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M, and Bedenne L: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol.* 2006 Oct; 24(28): 4620-5.
4. Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma. *Swedish Rectal Cancer Trial. Eur J Surg.* 1996 May; 162(5): 397-402.
5. Goldberg PA, Nicholls RJ, Porter NH, et al. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer.* 1994; 30A(11): 1602-6.
6. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med.* 1991 Mar 14; 324(11): 709-15.
7. Picciocchi A, Coco C, Magistrelli P, et al. Combined modality therapy of resectable high risk rectal cancer. *Rays.* 1995 Apr-Jun; 20(2): 182-9.
8. Carmichael J, Popiela T, Radstone D, et al. Randomized compara-

- tive study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2002 Sep; 20(17): 3617-27.
9. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2002 Sep 1; 20(17): 3605-16.
 10. Lembersky BC, Wieand HS, Petrelli NJ, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol*. 2006 May; 24(13): 2059-64.
 11. Bajetta E, Di Bartolomeo M, Buzzoni R, et al. Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomised phase II study. *Br J Cancer*. 2007 Feb; 96(3): 439-44.
 12. Delord JP, Bennouna J, Artru P, et al. Phase II study of UFT with leucovorin and irinotecan (TEGAFIRI): first-line therapy for metastatic colorectal cancer. *Br J Cancer*. 2007 Aug; 97(3): 297-301.
 13. Kono T, Ebisawa Y, Tomita I, et al. Phase II study of irinotecan, leucovorin, 5-fluorouracil and tegafur/uracil for metastatic colorectal cancer. *J Chemother*. 2005 Apr; 17(2): 224-7.
 14. Okabayashi K, Hasegawa H, Ishii Y, et al. Combination chemotherapy of biweekly irinotecan (CPT-11) plus tegafur/uracil (UFT) and leucovorin (LV) for patients with metastatic colorectal cancer: phase I/II study in Japanese patients. *Cancer Chemother Pharmacol*. 2009 Feb; 63(3): 501-7.
 15. Sadahiro S, Suzuki T, Maeda Y, et al. Phase I/II study of twenty-four-hour infusion of irinotecan in combination with oral UFT plus leucovorin for metastatic colorectal cancer. *Oncology*. 2009; 76(5): 338-41.
 16. Giralt J, Taberner J, Navalpotro B, et al. Pre-operative chemoradiotherapy with UFT and Leucovorin in patients with advanced rectal cancer: a phase II study. *Radiat Oncol*. 2008 Dec; 89(3): 263-9.
 17. Yasui M, Ikeda M, Sekimoto M, et al. Preliminary results of phase I trial of oral uracil/tegafur (UFT), leucovorin plus irinotecan and radiation therapy for patients with locally recurrent rectal cancer. *World J Surg Oncol*. 2006 Nov 22; 4: 83.
 18. Japanese Society for Cancer of the Colon and Rectum: General rules for clinical and pathological studies on cancer of the colon, rectum and anus. Tokyo Kanahara Publ Corp; 2013, p30-31.
 19. Hoff PM, Saad ED, Janjan N, et al. A phase I study. Preoperative UFT/leucovorin and radiation therapy in rectal cancer. *Oncology (Williston Park)*. 2000 Oct; 14(10 Suppl 9): 56-8.
 20. Kundel Y, Brenner B, Symon Z, et al. A phase II study of oral UFT and leucovorin concurrently with pelvic irradiation as neoadjuvant chemoradiation for rectal cancer. *Anticancer Res*. 2007 Jul-Aug; 27(4C): 2877-80.
 21. Rosenthal DI, Haller DG, Saltz L, Semple D, et al. Postoperative radiation therapy for rectal cancer combined with UFT/leucovorin. *Oncology (Williston Park)*. 2000 Oct; 14(10 Suppl 9): 59-62.
 22. Schiebe ME, Reese T, Wenz F, et al. Phase I study of oral uracil and Tegafur plus leucovorin and pelvic radiation in patients with recurrent rectal cancer. *Anticancer Drugs*. 2002 Nov; 13(10): 1005-9.
 23. Sato T, Hayakawa K, Tomita N, et al. A multicenter phase I study of preoperative chemoradiotherapy with S-1 and irinotecan for locally advanced lower rectal cancer (SAMRAI-1). *Radiat Oncol*. 2016 Aug; 120(2): 222-7
 24. Hofheinz RD, von Gerstenberg-Helldorf B, Wenz F, et al. Phase I trial of capecitabine and weekly irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer. *J Clin Oncol*. 2005 Mar; 23(7): 1350-7
 25. Ishihara S, Matsusaka S, Kondo K, et al. A phase I dose escalation study of oxaliplatin plus oral S-1 and pelvic radiation in patients with locally advanced rectal cancer (SHOGUN trial). *Radiat Oncol* 2015 Jan; 10: 24
 26. Ohue M, Hamaguchi T, Ito Y, et al. A phase I trial of preoperative S-1 in combination with oxaliplatin and pelvic radiation for lower rectal cancer with T4 and lateral pelvic lymph node metastasis. *Int J Clin Oncol*. 2015 Jun; 20(3): 543-8

Journal of the Anus, Rectum and Colon is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).