

# Preoperative Chemoradiation in Locally Advanced Rectal Cancer: A Comparison of Bolus 5-Fluorouracil/Leucovorin and Capecitabine

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## ABSTRACT

**Purpose:** To compare the acute toxicities, pathologic response, surgical margins, downstaging, local control, disease-free survival (DFS), and overall survival (OS) in locally advanced rectal cancer patients with preoperative radiotherapy (RT) with either concurrent bolus 5-fluorouracil (5-FU)/leucovorin (LV) or capecitabine (CA). **Materials and Methods:** Sixty patients who presented to our department with a diagnosis of locally advanced rectal cancer were treated with surgery following preoperative RT with either concurrent 5-FU/LV or CA between January 2008 and December 2011 were analyzed. **Results:** Median follow-up period was 38 months (range 3-61). Four patients (6.7%) had grade 3 gastrointestinal (GIS) toxicity during the course of chemoradiotherapy. The pathologic complete response rates were 8% with 5-FU/LV and 8.6% with CA ( $P = 0.844$ ). Also, 60% of the patients treated with 5-FU/LV and 37.1% with CA had downstaging of the T stage after chemoradiotherapy ( $P = 0.026$ ). The 5-year local control ( $P = 0.510$ ), distant control ( $P = 0.721$ ), DFS ( $P = 0.08$ ), and OS ( $P = 0.09$ ) rates were 80%, 80%, 59.4%, and 64.4%, respectively, for patients treated with 5-FU/LV and 85.7%, 82.9%, 74.8%, and 75.1%, respectively, for patients treated with CA. **Conclusion:** No significant differences were seen in the local control and distant recurrences and the survival among patients treated with pre-op RT and concurrent 5-FU/LV compared with those treated with pre-op RT and concurrent CA, except toxicities.

**Key Words:** Capecitabine, fluorouracil, locally advanced rectal cancer, radiotherapy

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Preoperative chemoradiotherapy currently serves as the standard treatment for locally advanced (T3, T4 with or without positive nodes) rectal cancer.<sup>[1]</sup> Patients treated with chemoradiotherapy had lower rates of local recurrence and toxicity and similar rates of survival compared with patients receiving postoperative chemoradiotherapy.<sup>[2]</sup> In rectal cancer treatment, the most frequently used drug in combination with radiotherapy (RT) is 5-fluorouracil (5-FU)/leucovorin (LV). The most common preoperative chemoradiotherapy regimes include 45-50.4 Gy of pelvic RT in addition to concurrent 5-FU in the first and last weeks of

RT or prolonged continuous infusion of 5-FU for the whole RT course.<sup>[3,4]</sup>

In the Intergroup 0144 trial, no significant differences were observed in the overall survival (OS) and relapse-free survival (RFS) among different regimens of 5-FU-based postoperative therapy.<sup>[5]</sup> On the other hand, in the Gastrointestinal Intergroup trial, patients treated with postoperative RT with concurrent protracted venous infusion of 5-FU had significantly higher rates of OS and RFS compared with those given bolus 5-FU.<sup>[3]</sup>

Continuous infusion has the biological advantage of prolonging the exposure of cells to 5-FU, thus improving antitumor activity, while its disadvantages include the need for indwelling central venous catheter and infusion pumps, with potential risks of complications such as infection, bleeding, venous thrombosis, and increased cost of treatment.<sup>[6,7]</sup> For this reason, we use bolus 5-FU routinely

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in our department for chemoradiotherapy of locally advanced rectal cancer. Furthermore, not all the patients can cooperate to take 5-day 5-FU treatment. In such cases, other fluoropyrimidines [capecitabine (CA), tegafur+uracil (UFT)] or thymidylate synthase inhibitors (raltitrexed) are applied.

CA is an orally administered fluoropyrimidine carbamate which is preferentially converted to active 5-FU through a three-step enzymatic pathway in the liver and in the tumor cells.<sup>[8,9]</sup> When administered on a twice-daily schedule, it may mimic the pharmacokinetics of a protracted 5-FU infusion. CA has been shown in two randomized trials to be at least equivalent in efficacy to bolus 5-FU/LV in the treatment of metastatic colorectal cancers.<sup>[10,11]</sup> It was associated with a higher rate of tumor response and lesser toxicity but equivalent survival when compared with bolus 5-FU/LV. Several phase II trials have used CA and preoperative RT for locally advanced rectal cancers and have shown that this combined treatment was well tolerated by patients and the rate of pathologic response was comparable to that of preoperative 5-FU/LV and RT.<sup>[12-15]</sup> Also, a recent randomized phase III trial in Germany confirmed that OS rates did not change when infused 5-FU/LV was replaced by CA during RT and adjuvant chemotherapy.<sup>[16]</sup>

CA cannot be used routinely in our country instead of 5-FU to decrease the probable toxicity of 5-FU. Barely CA is chosen, mainly depending on patient's economic status, since CA is not covered by the medical insurance system in our country. Generally, 5-FU is the only agent which is used.

This study was undertaken to compare the outcome of preoperative CA plus RT versus intermittent 5-FU/LV modulation plus RT in locally advanced rectal cancers. The goal of this study is to analyze the toxicity, pathologic response, relapse rate, and survival differences in locally advanced rectal cancer patients treated with either preoperative RT with concurrent 5-FU/LV or preoperative RT with concurrent CA.

## MATERIALS AND METHODS

### Patient selection

Sixty patients with histologically confirmed rectal adenocarcinoma and no evidence of distant metastasis or no previous history of pelvic RT, who were treated with preoperative RT with concurrent 5-FU/LV and concurrent CA followed by surgery between January 2008 and December 2011 were included.

Acute toxicity was graded using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria.

### Staging evaluation

Pretreatment evaluation included a complete history taking and physical examination assessed at baseline by chest X-ray, abdominal and pelvic computed tomography (CT) plus flexible endoscopy. Endoscopic ultrasonography (EUS) was performed for some patients. Clinical stage was determined based on the CT and EUS findings. The American Joint Committee on Cancer TNM 2002 system was used for staging. The clinical stage was T3 for 18 (72%) and T4 for 7 (28%) patients in the 5-FU/LV group and T3 for 28 (80%) and T4 for 7 (20%) patients in the CA group. The clinical stage was N0 for 20 (80%) and N+ for 5 (20%) patients in the 5-FU/LV group and N0 for 28 (80%) and N+ for 7 (20%) patients in the CA group.

### Treatment

RT began on the first day of chemotherapy and was administered five times per week with a daily fraction of 180 cGy. Initially, the entire pelvis was treated with 3- or 4-field techniques to 4500 cGy in a supine position. The superior border of the entire pelvis was placed at the lumbosacral junction. The inferior border was placed at 2 cm caudal to the gross tumor. The lateral field border was 1.5 cm outside the bony pelvic inlet. The anterior border of the lateral fields was 3 cm anterior to the gross tumor and shaped to include the internal iliac lymph nodes if T3 and the external iliac lymph nodes if T4. The posterior border of the lateral fields was extended to encompass the bony sacrum. Most patients received a boost to the primary tumor bed for a median total dose of 5040 cGy. A two-dimensional conventional technique or three-dimensional conformal technique was used according to the attending physician's choice.

Since the medical insurance system of our country does not finance the use of CA in preoperative chemotherapy for rectal cancer, when deciding on the treatment, CA was used in patients who could afford the treatment; meanwhile, to the ones who could not afford the price of the drug due to economic reasons, 5-FU/LV was preferred.

Either 5-FU (425 mg/m<sup>2</sup>) or LV (25 mg/m<sup>2</sup>) was administered during the first 4 days in the first week and then restarted for 3 days in the fifth week of the treatment course, or CA was administered concomitantly with RT at a dose of 825 mg/m<sup>2</sup> twice daily (bid) during the whole period of RT (days 1-33) without giving weekend breaks. CA doses were given every 12 hours with one of the doses administered 2 hours prior to irradiation. If RT was interrupted, chemotherapy was not administered.

Definitive surgery was scheduled 6 weeks after the completion of the chemoradiotherapy. The choice of surgical procedure was either low anterior resection (LAR) (50%) or abdominoperineal resection (APR) (50%).

In addition to concurrent chemotherapy, four courses of chemotherapy were planned postoperatively. This comprised either CA 1250 mg/m<sup>2</sup> bid on days 1-14 every 3 weeks for 4 cycles or bolus i.v. 5-FU 425 mg/m<sup>2</sup>/day and LV 20 mg/m<sup>2</sup>/day on days 1-5 of each cycle repeated every 4 weeks.

### Ethical consideration

Following the legal and penal codes in the country, it is mandatory to have a signature-bearing certificate of each patient stating their personal approval to be enrolled in such study.

### Statistical analysis

The patient characteristics, toxicities, downstaging, and sphincter preservation were compared among the two groups using Chi-square test, Fisher's exact test or Student's *t*-test, and Kruskal-Wallis test, for which *P* values less than 0.05 were considered to be statistically significant.

Kaplan-Meier method was used to estimate disease-free survival (DFS) and OS. Survival differences between the two groups were tested by log-rank test. Hazard ratios, 95% confidence intervals (CI), and *P* values were calculated. All statistical analyses were conducted using the SPSS (version 10.0) statistical software program. Cox regression analysis was used to determine the effective factors in DFS and OS.

## RESULTS

### Patient characteristics

The patient characteristics are shown in Table 1. Their median age was 55 (range 36-80) years.

### Acute toxicity

The highest grades of acute toxicity during chemoradiotherapy in each group are shown in Table 2. Patients treated with 5-FU/LV had a higher rate of grade 2 gastrointestinal toxicity compared to CA group patients (diarrhea, rectal pain/tenesmus, and mucositis) (65.2% and 34.3%, respectively, *P* = 0.008), whereas CA group had a higher rate of grade 1 dermatologic toxicity in comparison to 5-FU/LV group (20% and 4%, respectively, *P* = 0.030). Also, 5-FU/LV group had a higher rate of grade 1 hematologic toxicity (*P* = 0.030).

None of the patients required hospitalization or dose reduction, discontinuation, or other modification during chemoradiotherapy and chemotherapy.

### Surgery and pathologic response

No statistically significant difference was found in the rate of pathologic complete response [Table 3]. Tumor downstaging was determined by comparing pretreatment T stage (as defined by clinical, radiographic, and ultrasound staging)

**Table 1: Patient characteristics**

Characteristics	5-FU/LV		CA		<i>P</i>
	<i>n</i>	%	<i>n</i>	%	
Gender					
Male	20	80	25	71.4	0.503
Female	5	20	10	28.6	
Age, years	56 (range 39-76)		55 (range 36-80)		0.583
Median distance anal verge-tm (cm)	6.75		5.96		0.048
Pre-treatment HGB level (g)					
8-10	2	8	3	8.6	0.043
10-12	10	40	12	34.2	
12-14	7	28	10	28.6	
14-16	6	24	10	28.6	
Pre-operative TNM					
T3N0M0	15	60	22	62.9	0.266
T3N1M0	1	4	4	11.4	
T3N2M0	2	8	2	5.7	
T4N0M0	5	20	6	17.1	
T4N1M0	2	8	1	2.9	
Pathologic type					
Adenocarcinoma	22	88	31	89	0.585
Mucinous adenocarcinoma	3	12	4	11	
Grade					
Well differentiated	2	8	5	14.3	0.037
Moderately differentiated	18	72	28	80	
Poorly differentiated	5	20	2	5.7	

HGB: Hemoglobin, CA: Capecitabine, TNM: Primary tumor, Regional lymph nodes, Distant metastasis, FU: Fluorouracil, LV: Leucovorin

**Table 2: Worst grades of acute toxicity during chemoradiotherapy**

Toxicity G1 (%)	5-FU/LV (%)			CA (%)			<i>P</i>
	G1	G2	G3	G1	G2	G3	
Gastrointestinal	5 (20)	16 (64)	4 (16)	4 (11.4)	12 (34.3)	-	0.008
Hematologic	21 (84)	-	-	20 (57.1)	-	-	0.030
Dermatologic (hand-foot syndrome)	1 (4)	-	-	7 (20)	1 (2.8)	-	0.030

CA: Capecitabine, FU: Fluorouracil, LV: Leucovorin

**Table 3: Pathologic response to chemoradiotherapy**

Characteristics	5-FU/LV		CA		<i>P</i>
	<i>n</i>	%	<i>n</i>	%	
Pathologic complete response	2	8	3	8.6	0.844
Pathologic T stage					
<T1	5	20	4	11.5	0.844
T2	6	24	8	12.8	
T3	11	44	18	51.4	
T4	3	12	5	14.3	
Downstaging	15	60	13	37.1	0.026
Sphincter preservation	12	48	18	51.4	0.912
Positive surgical margin	6	24	7	20	0.585

CA: Capecitabine, FU: Fluorouracil, LV: Leucovorin

and the pathologic stage. The post-chemoradiation N-stage was not changed in the two groups. Although tumor downstaging was observed in each group, significant difference was found in the rate of downstaging in patients treated with 5-FU/LV (60%) compared with patients treated with CA (37.1%) ( $P = 0.026$ ).

Surgery of 12 (48%) of patients treated with 5-FU/LV consisted of sphincter-sparing surgery methods including LAR, and that of 13 patients consisted of APR (52%). Of the patients treated with CA, 18 (51.4%) underwent sphincter-sparing surgery including LAR. The other patients ( $n = 17$ ) were treated with APR (48.6%). There was no statistically significant difference in sphincter preservation rates between the two groups ( $P = 0.912$ ). There were no statistically significant differences between the groups in positive surgical margin rates after surgery ( $P = 0.585$ ).

In addition to acute toxicity of chemoradiotherapy, postoperative complications such as anastomotic leakage were not observed.

### Relapses and survivals

During a median follow-up period of 38 months (range 3-61), 10 patients (16.7%) had local recurrences and 11 patients (18.3%) had developed distant recurrences. Local recurrences were seen in five patients (20%) the 5-FU/LV group and in five patients (14.3%) in the CA group. There was no statistically significant difference between groups with respect to local recurrence rates ( $P = 0.510$ ).

Distant metastasis was seen in five patients (20%) who had been treated with 5-FU/LV and in six (17.1%) patients who had been treated with CA. Similar to metastasis rates, no statistically significant difference was found in metastasis frequency rates ( $P = 0.721$ ).

The OS rates for all patients were 80.2% and 70% after 3 and 5 years, respectively, and for the DFS, the rates were 75.7% and 67.1% after 3 and 5 years, respectively.

The 3-5 year DFS rates in the 5-FU/LV group were 76.3% and 59.4%, respectively, while in the CA group, the rates were 75.1% and 74.8%, respectively, ( $P = 0.08$ ). The 3-5 year OS rates in cases treated with 5-FU/LV were 81.1% and 64.4%, respectively, and were 79.2% and 75.1%, respectively, in cases treated with CA ( $P = 0.09$ ). There was no statistically significant difference between the DFS and OS rates in both groups.

All prognostic factors listed below for DFS and OS rates have been evaluated by univariate analysis and no statistically significant differences were found regarding age, gender, pretreatment hemoglobin level, toxicity, post-treatment TNM, histologic subgroups, grade, surgical experience,

time interval between RT and surgery, operation type, chemotherapy agent, and localization of tumor.

## DISCUSSION

5-FU is currently accepted as the standard cytotoxic agent for preoperative chemoradiotherapy of rectal cancer. Considering the disadvantages of continuous infusion, there are studies evaluating alternative agents. These are mainly oral agents. Although these studies demonstrated no significant difference compared to 5-FU applied either continuously or as bolus, toxicity differences were reported. Kim *et al.*<sup>[17]</sup> retrospectively reported that preoperative chemoradiation with oral CA is more tolerable with respect to side effects, and offers a more effective treatment modality than bolus 5-FU/LV, as measured by tumor downstaging, pathologic response, and sphincter preservation.

On the other hand, another retrospective trial demonstrated significant difference only in downstaging when CA was compared to continuous infusion (CI) 5-FU.<sup>[18,19]</sup> Another retrospective trial comparing CA with CI 5-FU showed no significant difference among these two agents in means of toxicity or survival.<sup>[1]</sup> Also, neoadjuvant radiochemotherapy with CA should be considered an effective treatment option to avoid local recurrence and also to improve survival in elderly rectal cancer patients.<sup>[20]</sup>

A recent randomized phase III trial in Germany confirmed that the endpoint OS rates did not change when infused 5-FU was replaced by CA during RT and adjuvant chemotherapy.<sup>[16]</sup> Likewise, in another study of Kim *et al.*,<sup>[21]</sup> no difference was found either in radiologic or pathologic outcomes between 5-FU and CA in post-therapeutic early stage.

Despite the similarity between the results with 5-FU and CA, since the toxicity is found to be more tolerable with CA, recently the researches combining CA with irinotecan and oxaliplatin are favored.<sup>[22,23]</sup>

Early results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04<sup>[22]</sup> and Lee *et al.*<sup>[23]</sup> trials did not confirm a significant improvement of short-term endpoints such as the pathologic complete response rate by addition of oxaliplatin or irinotecan. But results of several preoperative chemoradiotherapy phase I/II studies using CA/irinotecan or oxaliplatin at various dosages and schedules have shown encouraging tumor response rates and toxicity profiles.

In this study, distribution of these two groups is not balanced for the following reasons. While well-differentiated cases in CA arm are high, poorly differentiated cases are dominant in 5-FU/LV arm. There are differences in RT applications,

as two-field technique was used in FU arm and three- or four-field conformal RT was used in CA arm. Despite its disadvantages downstaging is significantly better with FL arm.

The main toxicities of bolus 5-FU injection are oral mucositis, gastrointestinal toxicity (diarrhea), myelosuppression, and skin toxicity. In a randomized phase III trial, CA was less toxic than bolus 5-FU/LV when administered to patients with advanced colorectal cancer.<sup>[11]</sup> Oral CA treatment results in a significantly lower rate of myelosuppression, diarrhea, stomatitis, nausea, and alopecia than bolus 5-FU/LV treatment. Grade 3 hand-foot syndrome developed more frequently after oral CA treatment than after bolus 5-FU/LV treatment. In patients receiving high-dose CI 5-FU/LV, hand-foot syndrome was a frequent side effect, but it did not significantly affect patients' quality of life or the delivery of the planned chemotherapy.<sup>[24]</sup> In this study, grade 2 leukopenia and thrombocytopenia occurred only in the bolus 5-FU/LV group, with no incidences of these toxicities in the oral CA group. The most commonly occurring grade 3 non-hematologic toxicities were diarrhea and grade 1 leukopenia and thrombocytopenia in the bolus 5-FU/LV treatment group, and hand-foot syndrome in the oral CA group. Statistically, there was less diarrhea and radiation dermatitis in the latter group.

The present study, examining short-term tumor responses, pathologic response rates, surgical margin status, local control rates, DFS, and OS, could not demonstrate any significant differences between CA and bolus injection of 5-FU/LV for preoperative chemoradiotherapy of locally advanced rectal cancer. Long-term results and prospective randomized trials are needed.

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