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Original Article

# Preoperative chemoradiotherapy with oxaliplatin and tegafur-uracil in locally advanced rectal cancer: Pathologic complete response rate and preliminary results of overall and disease-free survival in a single institute in Taiwan

Jeffrey Yung-Chuan Chao [a,b], Hwei-Ming Wang [c], Feng-Fan Chiang [c], Jing-Chin Lin [a,d], Chen-Fa Chang [a], Jia-Fu Lin [a], Hui-Ling Yeh [a,*]

[a] *Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[b] *Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[c] *Section of Colon and Rectal Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[d] *Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

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**Abstract**

*Background*: We conducted a Phase II study of biweekly oxaliplatin plus oral tegafur-uracil in the preoperative chemoradiotherapy (CRT) for locally advanced resectable mid-to-lower rectal cancer in our hospital, to evaluate the feasibility of this drug combination in tumor pathologic response, acute toxicity, local control, disease-free survival (DFS), overall survival (OS), and time to distant metastasis in an Asian cohort.
*Methods*: Twenty patients with histopathologically confirmed rectal cancer (Stage II–III) were enrolled in the study. Radiotherapy of 50 Gy was delivered in 25 fractions of 2 Gy, one fraction/day, five fractions/week, for 5 weeks. Oxaliplatin 55 mg/m$^2$ was administered intravenously for 60 minutes on Day 1 every 2 weeks, and tegafur-uracil 350 mg/m$^2$ was given orally everyday during the whole radiotherapy course, including holidays. Surgery was scheduled 6 weeks after completion of the preoperative chemoradiotherapy. The primary endpoint was to determine the pathologic complete response (pCR) rate after this neoadjuvant chemoradiotherapy. The secondary endpoint was to determine the treatment-related toxicity profile, local control, DFS, OS, and time to metastasis.
*Results*: All patients underwent a complete course of preoperative chemoradiotherapy. There was no local recurrence during the study period. The complete resection rate was 20/20 (100%) and the close resection margin rate was 3/20 (15%). The pCR rate was 8/20 (40%). During chemoradiotherapy, the most frequent toxicity was diarrhea 9/20 (45% of patients, grade 2 in 3/20, 15%). There were no grade 3 or higher hematologic or non-hematologic events or treatment-related deaths. The 3-year OS and DFS rates were 94.1% and 78.6%, respectively.
*Conclusion*: Preoperative chemoradiotherapy with oxaliplatin and tegafur-uracil was well-tolerated and achieved an excellent pCR in our patients with locally advanced mid-to-lower rectal cancer.


*Keywords:* chemoradiotherapy; oxaliplatin; preoperative; rectal neoplasm; tegafur-uracil

## 1. Introduction

Colorectal cancer is a major health problem in Taiwan. The annual incidence of colorectal cancer has increased up to 43.5% in the past 10 years, with >8000 new cases of colon cancer and >2600 new cases of rectal cancer each year. Because of the unique anatomic location of rectal cancer, it

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* Corresponding author. Dr. Hui-Ling Yeh, Department of Radiation Oncology, Taichung Veterans General Hospital, 1650, Section 4, Taiwan Boulevard, Taichung 407, Taiwan, ROC.
*E-mail address:* hlyeh@vghtc.gov.tw (H.-L. Yeh).

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tends to recur locally after surgical treatment alone. Total mesorectal excision (TME) can reduce the local recurrence rate to < 10%. Abdominoperineal resection is the standard treatment for distal rectal cancer. However, it has significant disadvantages of anal sphincter sacrifice with permanent colostomy and a high incidence of sexual and urinary dysfunction.

Although TME has markedly improved the local control of locally advanced distal rectal cancer, the addition of pelvic radiation concomitant with fluorouracil (5-FU) chemotherapy had provided further improvement in pelvic local control according to the Dutch trial.[1] Many Phase II studies have shown higher rates of complete pathologic responses after chemoradiotherapy compared with radiation alone.[2,3] The German Rectal Cancer Study Group Phase III study further demonstrated the advantages of preoperative chemoradiotherapy over postoperative chemoradiotherapy in acute toxicity, anal sphincter preservation, and local control.[4−6] Studies are now focused on the use of radiosensitizers in combination with 5-FU to determine whether this newly developed preoperative treatment will provide better results than the conventional 5-FU-based chemoradiotherapy. Tegafur-uracil is a composite drug composed of 100 mg tegafur and 224 mg uracil (molar ratio 1:4). It is an attractive oral form of 5-FU and is marketed as tegafur-uracil in Taiwan. Tegafur, a prodrug of 5-FU, is easily absorbed though the gastrointestinal tract and slowly metabolized to 5-FU, mainly in the liver. Tegafur given with radiotherapy for patients with rectal cancer showed significantly less hematologic toxicity without significant treatment outcome difference with 5-FU.[7] Uracil is an inhibitor of dihydropyrimidine dehydrogenase, the rate-limiting enzyme of 5-FU degradation. A stably high concentration of tegafur-uracil is expected to be maintained in the liver and in circulation. It has been approved for treatment of advanced gastric cancer and colorectal cancer, which are usually treated with 5-FU-based chemotherapy in Taiwan.

Oxaliplatin is a platinum derivative which has shown radiosensitizing properties and synergism with 5-FU. Clinical studies have shown high response rates for the combination of oxaliplatin with either 5-FU or radiation therapy. Furthermore, the addition of oxaliplatin to a biweekly regimen with 5-FU proved manageable and beneficial in patients with metastatic colorectal cancer.[8] Recently, several investigators have reported that the combination of oxaliplatin with fluoropyrimidines in preoperative chemoradiotherapy is associated with a pathologic complete response (pCR) of about 15−29% in locally advanced rectal cancer.[9−11]

To achieve downstaging and better resectability in locally advanced or low rectal cancer, preoperative chemoradiotherapy with 5-FU has become the standard of treatment. However, the pCR is still unsatisfactory. We conducted a Phase II study of biweekly oxaliplatin plus oral tegafur-uracil in the preoperative chemoradiotherapy for resectable rectal cancer in a single institute, to evaluate the tumor pathologic response, acute toxicity, local control, disease-free survival (DFS), overall survival (OS), and time to distant metastasis in an Asian cohort.

## 2. Methods

### 2.1. Study design and patients

This open-label, single arm, Phase II study was conducted in a single institute and approved by the hospital's institutional review board. Each patient provided written informed consent before participating in the study.

Eligible patients were those aged 18−75 years, with pathologically confirmed rectal adenocarcinoma with an inferior margin no more than 10 cm above the anal verge, including anorectal junction tumor, as assessed by a lower GI scope. The clinical stage was defined according to AJCC 2002 TMN staging by computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, chest X-ray, whole-body bone scan, or positron emission tomography (PET) scan. Further inclusion criteria were Karnofsky performance scale (KPS) ≥ 70%, and adequate hematological, liver, and renal functions.[12]

Exclusion criteria included metastatic disease when diagnosed, prior chemotherapy or radiotherapy to the pelvic area, other cancers, contraindication for administration of oxaliplatin or tegafur-uracil, pregnancy or nursing, and refusing radical operation after preoperative chemoradiotherapy.

### 2.2. Treatment plan

After urine voiding, the patients were advised to intake 300 mL of water. Thirty minutes later, the patients underwent CT simulation in the supine position with immobilization with a vacuum cushion. Identical urine voiding and immobilization procedures were taken for each fraction of radiotherapy.

$PTV_G$ was defined as gross tumor volume with 5−10 mm margin, and $PTV_C$ as clinical tumor volume (CTV) with 8−10 mm margin. Gross tumor volume consisted of gross rectal tumor and pelvic lymphadenopathy, and CTV consisted of internal iliac lymph node below the L5-S1 spine level, mesorectum, perirectal fat, and the presacral space. For T4 tumor, an external iliac lymph node was also included in CTV. Radiotherapy consisted of a total of 50−50.4 Gy to planning target volume of gross tumor ($PTV_G$) and 45 Gy to planning target volume of clinical and subclinical tumor volume ($PTV_C$) delivered as 10−15 MV photons in 25 fractions, of 2 Gy/fraction, five fractions/week, delivered by a seven-field intensity-modulated technique with five to seven fields. The treatment machine was a VARIAN Clinac 21EX, and planning software was Eclipse Version 10 (Varian Medical Systems Inc., Palo Alto, CA 94304, USA).

During the whole radiotherapy course, concurrent chemotherapy with oxaliplatin 55 mg/m$^2$ was administered intravenously for 60 minutes on Day 1 every 2 weeks, and tegafur-uracil 350 mg/m$^2$ was given orally every day, including weekends and holidays.

Radical surgery was performed in all of the patients according to a standardized technique 6−8 weeks after preoperative chemoradiotherapy was completed (Fig. 1). One of the two standard procedures, anterior resection with the TME

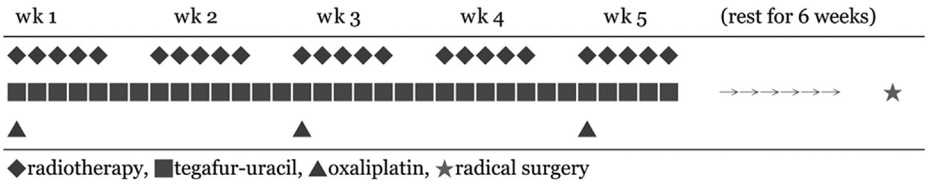


Fig. 1. Treatment course of preoperative chemoradiotherapy. Radiotherapy was delivered in 25 fractions, one fraction/day (five fractions/week) for 5 weeks. Oxaliplatin was administrated intravenously for 60 minutes on Day 1 every 2 weeks, and tegafur-uracil was given orally during the whole radiotherapy course, including holidays.

technique or abdominoperineal extirpation, was performed according to tumor extension and individual situation.

During radiotherapy, side effects were monitored and complete blood cell count/differential blood count (CBC/DC) and sequential multiple biochemical analysis of blood (SMA) were checked weekly. NCI Common Toxicity Criteria and Toxicity Criteria of the Radiation Therapy Oncology Group were employed in the evaluation of toxicity. Therapeutic effects were determined by pathological evaluation of radical surgery.

Pathologic response of tumor regression (TRG) was graded according to a method described by Dworak et al[13] for the assessment of the pathologic response after preoperative chemoradiotherapy in rectal cancer on a scale from zero to four, based on the presence of residual tumor cells and the extent of fibrosis.

### 2.3. Statistical considerations

The primary endpoint of this study was to determine the efficacy of oxaliplatin, tegafur-uracil, and radiotherapy by pathologic response, and the second endpoint was to determine the toxicity associated with this combination, local control, DFS, OS, and time to metastasis. The treatment efficacy was primarily measured by tumor regression grade. Descriptive statistics were reported as proportions and medians. Kaplan–Meier analysis was used to estimate DFS and OS.

## 3. Results

### 3.1. Patient characteristics

A total of 20 patients were enrolled in the study from January 2008 to May 2009. There were 11 males and nine females. All patients had newly diagnosed rectal cancer and no evidence of distant metastases when diagnosed. The median age was 60.5 years (range 26–70 years). The clinical T and N stages were determined by CT ($n = 14$) or MRI ($n = 6$) scan according to AJCC 2002 staging system. Clinical T stages were T2(4), T3(12), and T4(6), and clinical N stages were N0(8), N1(9), N2(5), as shown in Table 1. In 15 patients, the tumor was located 0–5 cm from the anal verge. Patient characteristics are listed in Table 1.

### 3.2. Response and survival

As shown in Table 2, tumor regression grade (TRG) 4 was found in eight patients (40%), TRG3 in four patients (20%), TRG2 in seven patients (35%), and TRG0 in one patient (5%). With a median follow-up of 38 months, the 3-year OS rate was 94.1% and the 3-year DFS rate was 78.6%. DFS and OS are shown in Fig. 2. Sixteen patients (80%) were disease-free and four patients (20%) relapsed, all with distant metastasis alone. None of the patients developed local recurrence. First-diagnosed distant metastases were located in the liver (two patients), lung (two patients), and brain (one patient). One patient was diagnosed as having distant recurrence with simultaneous brain and lung metastasis. In distant-failure patients, median time to distant recurrence was 7.5 months.

### 3.3. Treatment compliance

All patients received the scheduled radiotherapy dose to $PTV_G$ and $PTV_C$. The median treatment time was 35 days (range 32–43 days). All patients received the planned oxaliplatin and tegafur-uracil doses. The median time from completion of chemoradiotherapy to surgery was 43 days (range 33–50 days). Eleven patients underwent coloanal anastomosis, five patients underwent lower anterior resection of rectal tumor, and four patients underwent abdominoperineal resection with permanent colostomy. The sphincter-preservation rate was 16/20 (80%) in all patients, and 9/13 (69%) in patients with tumor seated $\leq 5$ cm from the anal verge.

Table 1
Patient characteristics.

| | No. of patients | % |
|---|---|---|
| Patients | 20 | 100 |
| Age (y) | | |
| Median (range) | 60.5 (47–70) | |
| Sex | | |
| Male | 11 | 55 |
| Female | 9 | 45 |
| BMI (kg/m$^2$) | | |
| Median (range) | 24 (18–28) | |
| Performance status | | |
| Karnofsky | | |
| 90 | 7 | 35 |
| 80 | 13 | 65 |
| TN clinical staging | | |
| T2N0 | 3 | 15 |
| T3N0 | 3 | 15 |
| T4N0 | 1 | 5 |
| T3N1-2 | 9 | 45 |
| T4N1 | 4 | 20 |
| Distance from anal verge | | |
| ≤5 cm | 13 | 65 |
| 5–8 cm | 7 | 35 |

Table 2
Parameters after preoperative chemoradiotherapy and radical surgery ($n = 20$).

| Parameter | No. of patients | % |
|---|---|---|
| Tumor regression grade | | |
| 0 | 1 | 5 |
| 2 | 7 | 35 |
| 3 | 4 | 20 |
| 4 | 8 | 40 |
| Types of surgery | | |
| Low anterior resection | 5 | 25 |
| Coloanal anastomosis | 11 | 55 |
| Abdominoperineal resection | 4 | 20 |
| Number of harvested lymph nodes | | |
| Median (range) | 10.5 (2–24) | |
| Surgical complication | | |
| Anastomosis leakage | 1 | 5 |
| Mortality | 0 | 0 |

Surgical complications consisted of one anastomotic leakage with pus formation. The anastomosis condition was controlled after antibiotics treatment and wound debridement, and closure of ileostomy was performed smoothly 6 weeks later.

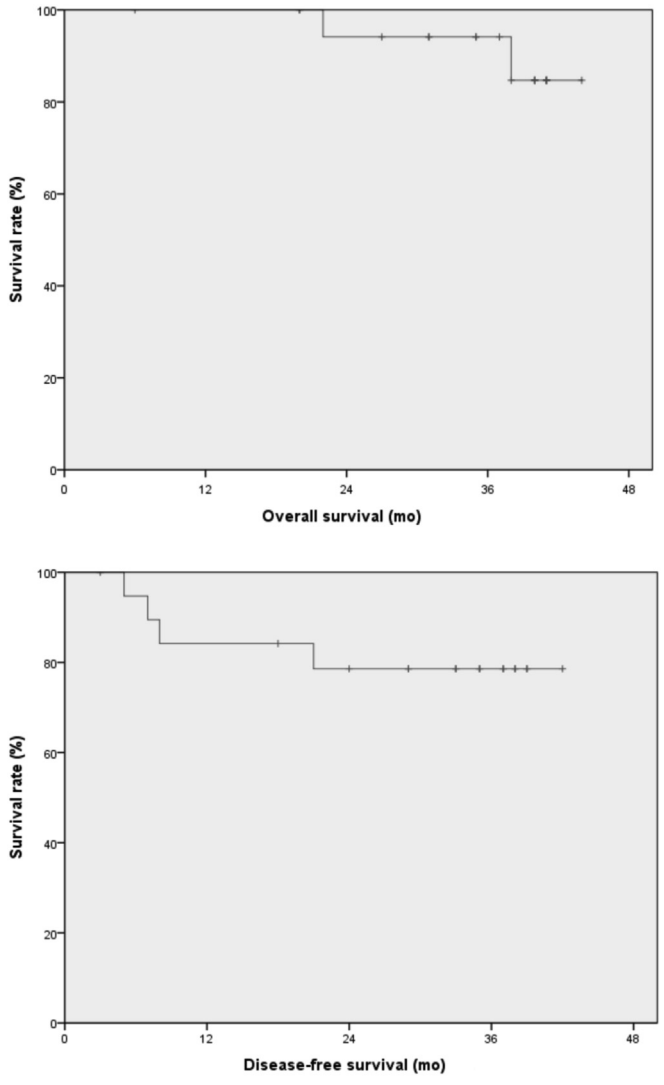


Fig. 2. Overall survival (upper) and disease-free survival (lower) for all patients ($n = 20$).

### 3.4. Toxicity

Toxicities were mild to moderate in intensity and easily managed. There were no grade 3 or higher hematologic or non-hematologic events. The most frequent toxicity was diarrhea (9/20, 45% of patients, grade 2 in 3/20, 15%), followed by asthenia (5/20, 25%), neutropenia (5/20, 25%), constipation (5/20, 25%), nausea (2/20, 10%), and vomiting (2/20, 10%), shown in Table 3.

## 4. Discussion

The response of preoperative chemoradiotherapy in rectal cancer has a significant impact on prognosis. Many clinical trials have assessed the treatment effects of preoperative chemoradiotherapy. Oxaliplatin is widely used in the postoperative adjuvant setting, and has also been applied in preoperative treatment.[14]

Some clinical trials showed that the addition of oxaliplatin increased toxicity without primary tumor response benefit. Aschele et al[15] conducted a Phase III trial in 2011, in which radiotherapy was administrated concurrently with daily infusional 5-FU 225 mg/m$^2$ and, for the experimental arm, additional weekly intravenous oxaliplatin 60 mg/m$^2$ for 2 hours. After preoperative CRT, the pCR rates were both 16% with or without oxaliplatin. The grade 3–4 toxicity of the oxaliplatin group was 24%, and that of the control group was 8%. The compliances for radiotherapy and chemotherapy were only 84% and 66%, respectively. Poor compliance indicated that the chemotherapy regimen was too toxic, so treatment was discontinued. This might have compromised primary tumor response and diminished the benefit of oxaliplatin.

By contrast, some clinical trials showed positive results. In the German CAO/ARO/AIO-04 randomized Phase III trial, chemotherapy with infusional 5-FU (250 mg/m$^2$ Days 1–14 and Days 22–35) and oxaliplatin (50 mg/m$^2$ Day 1, Day 8, Day 22, and Day 29) was given concurrently with radiotherapy.[16] Better pCR was observed in the oxaliplatin group than the control group (17% vs. 13%, $p = 0.038$). Although the grade 3–4 toxicities of the control group and oxaliplatin group were similar (20% vs. 23%), the compliances of radiotherapy and chemotherapy were 94% and 85%, respectively in the oxaliplatin group.

Table 3
Toxicity profile ($n = 20$).

| Toxicity | NCI-CTC grade (%) | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Neutropenia | 4 (20) | — | — | — |
| Febrile neutropenia | — | — | — | — |
| Thrombocytopenia | — | — | — | — |
| Diarrhea | 6 (30) | 3 (15) | — | — |
| Constipation | 4 (20) | — | — | — |
| Nausea | 2 (10) | — | — | — |
| Vomiting | 2 (10) | — | — | — |
| Fatigue | 5 (25) | — | — | — |
| Neurotoxicity | 4 (20) | — | — | — |

NCI-CTC = National Cancer Institute Common Toxicity Criteria.

As a radiosensitizer, chemotherapy dose reduction is necessary to achieve a tolerable combination of treatments. Treatment compliance is important to gain treatment benefit. In our study, oxaliplatin 55 mg/m$^2$ every 2 weeks and daily tegafur-uracil 250−350 mg/m$^2$ were given concurrently with radiotherapy and all of our patients tolerated the treatment well. There were no grade 3 or above adverse events. The only hematologic side effect was neutropenia (4/20, 20%), and all of the cases were grade 1 and short-lasting, without neutropenic fever. The most common side effect was grade 1−2 diarrhea, which was manageable with medication. Only grade 1 neurotoxicity was observed in four (20%) patients. The profiles of side effects were consistent with those in previous studies. All patients completed the full course of chemotherapy and radiotherapy. The treatment results were compatible with those of similar studies. After preoperative chemoradiotherapy, the pCR rate, and the 3-year OS and DFS rates were 8/20 (40%), 94.1%, and 78.6%, respectively, which were markedly better than those (12.5%, 4-year 74.5%, and 4-year 70.3%) of infusional 5-FU of our institute.[17] After follow-up for 3 years, the OS and DFS rates were 94.1% and 78.6%, respectively.

The failure pattern in our study was distant metastasis in four patients. After preoperative chemoradiotherapy and radical surgery, more intensive adjuvant treatment, such as chemotherapy, should be considered for high-risk patients, to achieve better disease control and improve OS.

Although good treatment responses, limited side effects, and rare surgical complications were noted in this Phase II study, it was conducted in a single institute and only included 20 patients. Further randomized Phase III trials with larger cohorts are suggested to demonstrate the benefit of the addition of oxaliplatin in preoperative chemoradiotherapy for rectal cancer.

In conclusion, preoperative chemoradiotherapy with oxaliplatin and tegafur-uracil was a well-tolerated treatment regimen that achieved an excellent pCR in 40% of patients with locally advanced mid-to-lower rectal cancer. Further trials are needed to confirm the benefits of adding oxaliplatin in preoperative chemoradiotherapy for rectal cancer.

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