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# Pre-Operative Chemoradiotherapy With Oral Tegafur-Uracil and Leucovorin for Rectal Cancer

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**Background:** To evaluate the efficacy and toxicity of pre-operative radiotherapy (RT) combined with oral tegafur-uracil (UFUR) plus leucovorin (LV) in rectal cancer.

**Patients:** Sixty-five patients with rectal adenocarcinoma (clinical staged T2-4N0-2M0) received pelvic RT of 45 Gy in 20 fractions over 28 days. Concurrent chemotherapy consisted of UFUR (200 mg/m$^2$/day) and LV (45 mg/day) on day 1–28. UFUR (250 mg/m$^2$/day) and LV were continued on day 36–63. Surgery was performed on day 70.

**Results:** Sixty-three patients completed the concurrent chemoradiotherapy (CCRT) and 56 received curative or palliative surgery. Among the 52 patients receiving curative resection, downstaging (DS) occurred in 39 (75%), pathological complete response in 13 (25%), and sphincter preservation was achieved in 16 of 29 (55%) with lower-seated tumors. With a median follow-up time of 33 months, local failure developed in 4 (8%) and distant metastases occurred in 7 (14%). The 3-year overall survival was 92% and disease-free survival 76%. For all 65 patients, grade 3–4 diarrhea developed in 6 (9%) and grade 3–4 leucopenia observed in 2 (3%).

**Conclusions:** Oral UFUR + LV administered with pre-operative RT are effective in tumor DS, pathological complete response, and sphincter preservation with tolerable toxicity in rectal cancer.

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KEY WORDS: **rectal cancer; pre-operative chemoradiotherapy; tegafur-uracil; leucovorin**

## INTRODUCTION

In treating rectal cancer, neoadjuvant radiotherapy (RT) with or without chemotherapy may be effective in improving resectability for locally advanced disease [1–4], sphincter preservation [5–7], and improved survival [8]. Pre-operative radiation combined with chemotherapy may be more efficient in downstaging (DS) of locally advanced rectal cancer than radiation alone [9–11]. 5-fluorouracil (5-FU) plus leucovorin (LV) is the most commonly used chemotherapy regimen for this disease [12,13]. Typically, these are administered intravenously (IV), either bolus or continuous infusion [14,15].

Oral tegafur is a prodrug of 5-FU. Uracil competes with 5-FU for the enzyme dihydropyrimidine dehydro-

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genase (DPD), which converts 5-FU into its inactive metabolite. The oral administration of tegafur and uracil combined in a 1:4 molar ratio (UFT or UFUR) simulates the continuous IV administration of 5-FU [16,17]. It was the idea that oral UFT plus LV could be given with pre-operative RT, avoiding the cost of central venous catheter placement, infusion pumps, and other ancillary costs.

A phase I study of pre-operative UFT plus LV along with radiation therapy (RT) suggested that the maximum tolerated dose of UFT was 350 mg/m$^2$/day with 90 mg/day of LV. Diarrhea was the dose-limiting toxicity [18]. Phase II trials utilizing UFT at a dose of 300–350 mg/m$^2$/day with oral LV (15–30 mg/day), combined with pre-operative RT of 45–50.4 Gy revealed similar tumor response and DS rates as those using 5-FU by IV route [19,20]. Again, diarrhea was the most frequent and serious toxic event reported in those phase I–II trials. The toxicity associated with UFT chemoradiation of rectal cancer might be dose dependent [20]. On the other hand, lower dose of UFT (400 mg daily) had been used with acceptable toxicity in the neoadjuvant or adjuvant setting for colorectal cancer, and improved disease-free survival could be obtained than surgery alone [21,22]. However, it is still unknown whether diarrhea can be reduced and anti-cancer activity can be maintained if the dose of UFT is reduced when combined with LV and RT.

We present our experience with a lower dose regimen of oral tegafur-uracil (200 mg/m$^2$/day, equal to 300 or 400 mg/day for our patients) combined with LV (45 mg/day) and pre-operative radiation (45 Gy) for rectal cancer patients. Tegafur-uracil was continued between RT and surgery with slightly elevated dose (250 mg/m$^2$/day). The efficacy and toxicity of the regimen were evaluated in this study.

## PATIENTS

Patients with histologically confirmed primary rectal adenocarcinoma were recruited. To qualify for enrollment, the primary tumor must be either locally advanced ($\geq$T3 by AJCC staging system) or lower seated ($<$6 cm from anal verge when the tumor was in T2 stage). The tumor should be treatable by conventional RT treatment portals with no evidence of distant metastases. The Eastern Cooperative Oncology Group performance status was of 0–2. Other criteria included: no prior chemotherapy or RT; no other malignancy; absolute granulocyte count higher than 1,500/mm$^3$; platelet count greater than 100,000/mm$^3$; bilirubin, transaminases, and creatinine levels $<$1.5-fold of the upper normal limit.

Pre-treatment evaluation included a complete history and physical examination, complete blood count, liver function tests, and carcinoembryonic antigen (CEA) level determination. Computer tomography (CT) scan or magnetic resonance imaging (MRI, 1.5-T Siemens Vision scanner with pelvic array coil and intrarectal tube) and proctoscopy were used to evaluate the primary disease. Chest X-ray, abdominal ultrasonography, and whole body bone scan were done for systemic evaluation. Informed consent was obtained from all patients.

## METHODS

### Treatment Protocol

Radiation therapy was administered with a linear accelerator producing 10 MV X-rays (Clinac 2100 C, 2100 CD, Varian, Palo Alto, CA). In cases with mid-to-upper rectal lesions ($\geq$6 cm from anal verge), the entire pelvis was treated with AP-PA plus bilateral portals daily. The superior margin was at the L5-S1 junction or higher for the sigmoid-rectal junction tumor; the lateral margins were 1.5 cm lateral to the widest bony margin of the true pelvic sidewall. The inferior margin was at least 3 cm below the primary tumor or at the inferior aspect of the obturator foramina, depending on which was the most inferior. For the lateral portals, the upper and lower limits coincided with the AP-PA fields. The anterior margin was located behind the symphysis pubis. If the urinary bladder or prostate was involved, the anterior margin was modified to include the urinary bladder and external iliac lymph nodes. The posterior margin was 0.5 cm behind the posterior surface of the sacrum and coccyx.

For lower-seated ($<$6 cm from the anal verge) rectal tumors, the three-field (patient's posterior and bilateral) technique was used. In these cases, only the true pelvis underwent irradiation. The relative weighting of the bilateral versus posterior fields was 1:1:2, and 45-degree wedges were used for the bilateral fields. The inferior margin would include the perineum, if the tumor was very low-seated (located less than 3 cm from the anal verge). Oral contrast media for small intestine was used routinely during simulation. In order to exclude the small bowel from the radiation volume, patients were routinely treated in a prone position with a homemade ''belly board.'' The upper margins of the radiation fields were coincided with the lower margin of the opening ($26 \times 28$ cm$^2$) of the board. Radiation therapy was delivered once per day with a 2.25-Gy fraction, 5 days per week. Total dose was 45 Gy over 4 weeks. The radiation dose was prescribed to the 95% isodose line encompassing the treated volume.

Concurrent chemotherapy was administered from day 1 to 28, during the entire course of RT. The dose of UFUR (TTY Biopharm, Taipei, Taiwan) was initially 200 mg/m$^2$/day. The total daily dose was divided into three doses per day. The dose of LV (Wyeth Lederle Laboratories, Taipei, Taiwan) was 45 mg/day in three divided doses. The patients were monitored with an interview, physical

examination, and complete blood count every week. The oral chemotherapy was continued after RT with a dose of 250 mg/m$^2$/day in another 28-day cycle on day 36–63.

Surgical resection was scheduled at 6–8 weeks after completion of RT. Distal safety margin rule of 2 cm was followed, and tumor-free margin was obtained for every potentially curative operation. Pathological staging was available in these patients and compared with the initial clinical stages.

### Toxicity

The common toxicity criteria (CTC) version 2.0 from National Cancer Institute was used to evaluate the toxicity of our chemoradiotherapy [23].

### Statistical Analysis

Overall survival was calculated from the date of entering this study to death. Disease-free survival was calculated from the date of surgery to failure. The disease-free survival and overall survival rates were calculated by the Kaplan–Meier method. Log-rank test was used for comparison of survival curves. Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS version 11.0, Chicago, IL). Results were considered significant with *P*-values less than 0.05.

## RESULTS

### Patient Characteristics

From May 2000 to August 2002, 65 patients were enrolled in this protocol. The patient characteristics are listed in Table I. Totally 42 of 65 (65%) patients received MRI, and the other 23 (35%) received CT scan to determine their clinical T and N stages.

**TABLE I. Patient Characteristics**

| | |
|---|---|
| No. of patients | 65 |
| Sex (male:female) | 47:18 |
| Median age (range) in years | 63 (42–86) |
| Median size (range) in cm | 4.5 (1.5–9.5) |
| Tumor pathology: adenocarcinoma | 65 |
| Preoperative staging (%) | |
| T2N0 | 9 (14) |
| T3N0 | 10 (15) |
| T4N0 | 3 (5) |
| T2N+ | 4 (6) |
| T3N+ | 29 (45) |
| T4N+ | 10 (15) |
| Median distance from anal verge (range) in cm | 5 (0.5–15) |
| Location (%) | |
| Lower third | 33 (51) |
| Middle third | 29 (45) |
| Upper third | 3 (5) |

### Efficacy

Fifty-six patients completed the full course of concurrent chemoradiotherapy (CCRT) and following operations, while nine patients did not, including three lost to follow-up, three refusals to operation, one medically unfit for operation, and two occurrences of grade IV toxicity during the CCRT. Disease progression after CCRT was found in four patients, including one of liver metastasis and three of peritoneal seeding found at exploration. Two of these four patients received abdomino-perineal resections (APR), the other one Hartmann procedure, and the final one colostomy. Among the 52 curative resections, there were 37 (71%) low anterior resections (LARs) and 15 (29%) APR, and there was no surgical mortality.

Table II demonstrates the post-treatment pathological stages of 52 patients comparing with pre-treatment clinical stages. MRI was done in 36 cases (69%) within this group. DS for the primary site occurred in 26/52 (50%) patients. If DS of the lymph nodes was also calculated, the total DS rate was 39/52 (75%). Pathological CR (pCR) was seen in 13/52 (25%) cases. The percentage of pCR for clinical T2, T3, and T4 cases were 25%, 28%, and 10%, respectively. Clinical T3 cases had the highest incidence of pCR (28%) but clinical T4 patients had the highest rate of T-DS (60%).

Sphincter-reservation surgery was usually difficult to perform when the tumor is lower-seated. For the 29 patients with tumor located less than 6 cm from the anal verge and initially not considered as candidates for sphincter-reservation surgery, 16 of them (55%) finally received LAR after CCRT. For those 26 patients with higher tumor ($\geq$6 cm from anal verge), 4 (15%) still received permanent colostomy.

The median follow-up time of the patients was 33 months (range 19–46). Among the 52 patients receiving pre-operative CCRT and curative surgery, 4 (8%) had local failures. A curve of actuarial local control was shown in Figure 1. Distant metastases including liver (two cases), lung (2), adrenal glands (1), brain (1), and inguinal lymph node (1) were found in 7 of 52 (14%) cases receiving complete treatment. Two patients had synchronous local and distant metastases. The median time between surgery and distant failure was 7 (range 3–28) months. On the other hand, none of our patients with

**TABLE II. Downstaging Results in 52 Patients**

| Clinical stage | Pathological stage | | | | | Downstaging (%) |
|---|---|---|---|---|---|---|
| | ypT0 | ypT1 | ypT2 | ypT3 | ypT4 | |
| T2 (12) | 3 | 2 | 5 | 2 | 0 | 5/12 (42) |
| T3 (32 | 9 | 1 | 5 | 17 | 0 | 15/32 (47) |
| T4 (8) | 1 | 0 | 1 | 4 | 2 | 6/8 (75) |
| Total | 13 | 3 | 11 | 23 | 2 | 26/52 (50) |

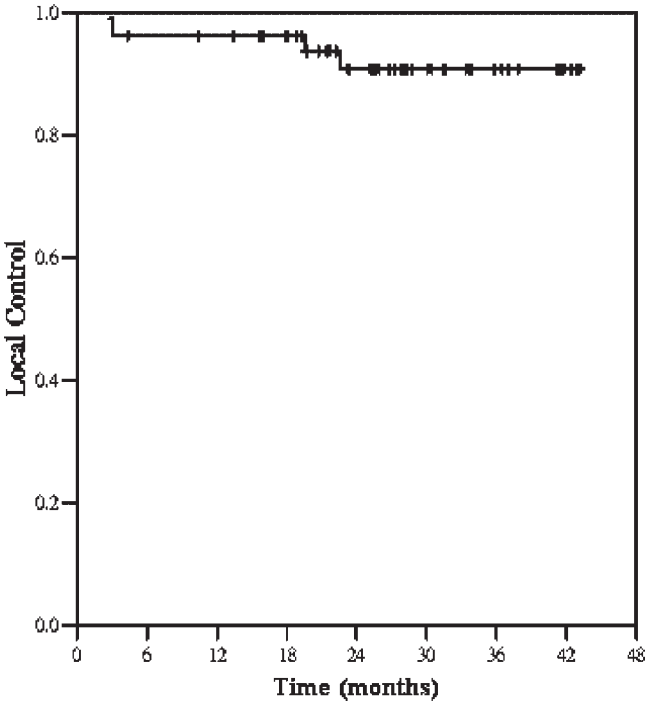


Fig. 1. Actuarial local control of 52 patients receiving chemoradiation and curative surgery.

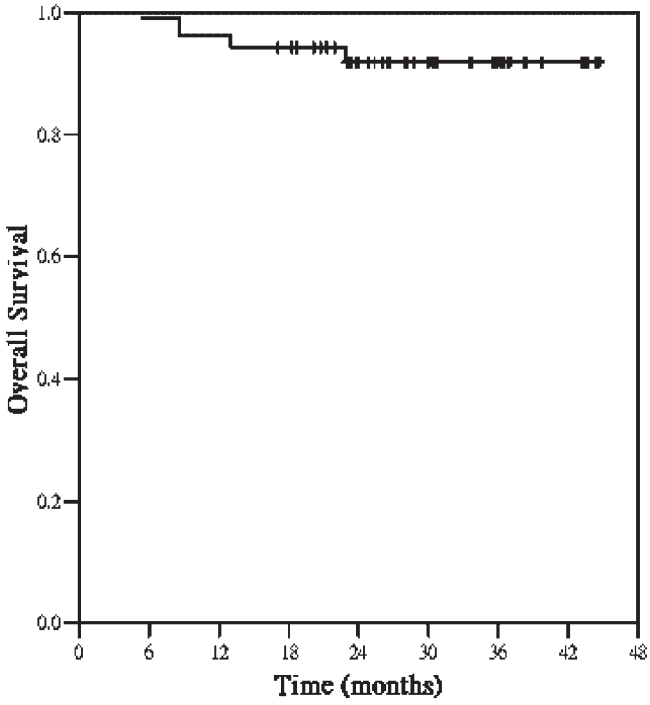


Fig. 2. Overall survival of 52 patients receiving chemoradiation and curative surgery.

pCR had any treatment failure. The 3-year overall survival curve for the 52 patients is shown in Figure 2 and disease-free survival curve in Figure 3. The 3-year overall survival rate was 92% and disease-free survival was 76%.

### Toxicity

The acute toxicity related to chemoradiotherapy is listed in Table III. Only two of these patients could not complete CCRT due to severe (grade 4) toxicity. One was leucopenic fever and another was diarrhea. Diarrhea was the most common side effects with 77% experiencing grade 1 or 2. However, only six patients (9%) had grade 3–4 diarrhea. Most of this side effect could be managed at the OPD. Nausea and vomiting were seldom observed (two patients). There was no oral mucositis (stomatitis), hand-foot syndrome, or alopecia. Grade 1–2 anemia and leukopenia were seen in 12 (18%) and 13 (20%), respectively. Two patients (3%) had grade 4 leukopenia. One of them could not finish CCRT and dropped out of this study. He remained alive and received curative surgery after his recovery. Another patient had transient grade 4 leukopenia after completion of CCRT but recovered completely without delay of subsequent chemotherapy and surgery.

Table IV listed the post-operative complications. Two patients (4%) experienced an anastomotic leakage of his J pouch and one patient had small bowel obstruction after LAR. All received salvage surgery. For anal sphincter function after anus preservation surgery, only one patient had obvious stool incontinence. Generally, all the other patients had fair to good stool continence.

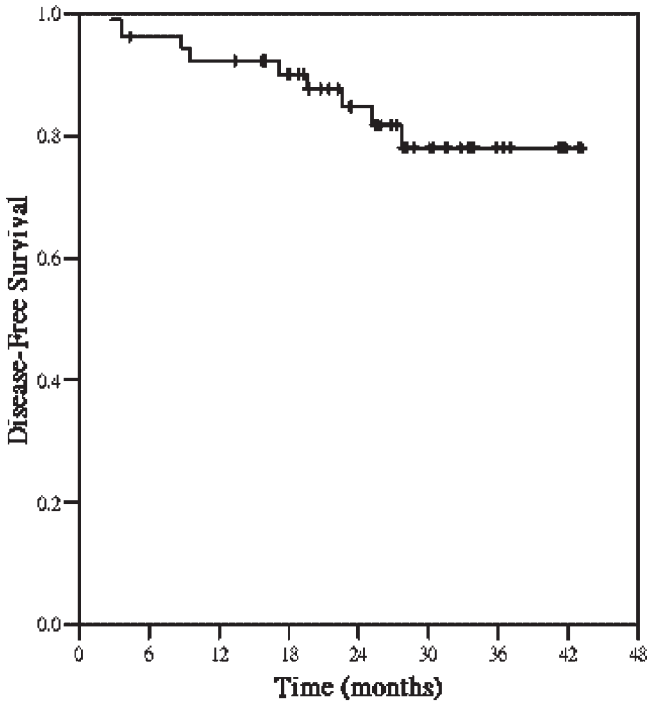


Fig. 3. Disease-free survival of 52 patients receiving chemoradiation and curative surgery.

**TABLE III. Toxicity (%) in 65 Patients**

| Grade | 1/2 | 3 | 4 |
|---|---|---|---|
| Hematologic | | | |
| Leucopenia | 13 (20) | 0 | 2 (3) |
| Thrombocytopenia | 2 (3) | 0 | 0 |
| Anemia | 12 (18) | 2 (3) | 0 |
| Non-hematologic | | | |
| Diarrhea | 50 (77) | 4 (6) | 2 (3) |
| Dysuria | 19 (29) | 1 (2) | 0 |
| Radiation dematits | 27 (42) | 0 | 0 |
| Nausea/vomiting | 2 (3) | 0 | 0 |
| Stomatitis | 0 | 0 | 0 |
| Hand-foot syndrome | 0 | 0 | 0 |
| Alopecia | 0 | 0 | 0 |

## DISCUSSION

The commonly used dosage of tegafur-uracil combined with LV for colorectal cancer is 300 mg/m$^2$/day or above [19,20,24]. However, modification of dosage (400 mg/d) has been used as adjuvant or neoadjuvant treatment for this disease [21,22]. This reduced dosage was also utilized in combination with LV (45 mg/day) for elderly patients with advanced colorectal cancer. Five percent of these patients still had CR and 12% had PR [25]. UFT 200 mg/ m$^2$/day combined with LV (90 mg/day) and hyperfractionated RT was well tolerated in advanced head and neck cancer [26]. Because more than one-third (23/65) of the patients entering this study were 70 years or older and the larger fraction size of the concurrent RT (2.25 Gy/day), modification of the dosage of UFUR was an intended way to improve tolerability.

Preoperative RT (45 or 50.4 Gy) combined with UFT (300–350 mg/m$^2$/day) plus LV [19,20] or UFT (400 mg/m$^2$/day) alone [27] were reported to be as effective as preoperative RT (45–60 Gy) and continuous venous infusion of 5-FU for rectal cancer patients [1,3,5,7,28,29]. The results of this study (DS of 75% and pCR of 25%) are also comparable to those of 5-FU by intravenous route or UFT of higher dosage (Table V). Some may argue that there were 13 T2 patients included here, and that would help obtaining this good result. However, there was no significant difference of DS and pCR rate between T2 and T3 in this study. Prolonged use of increased dosage to

**TABLE IV. Post-Operative Complications (%)**

| | |
|---|---|
| Delayed wound healing | 5 (10) |
| Anastomotic leakage of J pouch | 2 (4) |
| Chronic rectal bleeding | 2 (4) |
| Small intestine obstruction | 1 (2) |
| Ureter stricture | 1 (2) |
| Stool incontinence[a] | 1 (2) |

[a]In anus preservation surgery.

**TABLE V. Pre-Operative Chemoradiation for Rectal Cancer**

| Study (year) | Stage | Concurrent chemotherapy | RT dose (Gy) | pCR (%) | DS (%) | SP (%) | OS (%) | DFS (%) |
|---|---|---|---|---|---|---|---|---|
| Videtic et al. (1998) [1] | T4Nx | 5-FU CI | 54 | 13 | 90 | NR | 60 (3-year) | NR |
| Janjan et al. (1999) [5] | T2–4N0-2 | 5-FU CI | 45 | 27 | 62 for T | 59 | NR | NR |
| Rich et al. (1995) [7] | T3Nx | 5-FU CI | 45 | 29 | NR | 68 | 83 (3-year) | NR |
| Mehta et al. (2001) [28] | T3–4N0-1 | 5-FU CI | 50.4–54 | 33 | 63 for T or N | NR | NR | NR |
| Ngan et al. (2000) [29] | T3–4N0-2 | 5-FU CI | 50.4 | 16 | 51 for T | 61 | NR | NR |
| Torre et al. (1999) [19] | T3–4N0-2 and recurrence | Oral UFT (300 mg/m$^2$/day) + LV | 45 | 18 | 71 for T | NR | 61 (2-year)[a] | 54 (2-year)[a] |
| Uzcudun et al. (2002) [20] | T3–4N0-2 | Oral UFT (300 or 350 mg/m$^2$/day) +LV | 50.4 | 13 | 60 for T or N | 60 | 90 (3-year) | 83 (3-year) |
| Fernandez-Martos et al. (2004) [27] | T2–4N0-2 | Oral UFT (400 mg/m$^2$/day) | 45 | 15 | 54 for T | 25 | 75 (3-year) | 72 (3-year) |
| Wang et al. | T2–4N0-2 | Oral UFUR (200 mg/m$^2$/day) + LV | 45 | 25[b] | 75 for T or N[b] | 55[c] | 92 (3-year)[b] | 76 (3-year)[b] |

RT, radiotherapy; pCR, pathological complete response; DS, downstaging; SP, sphincter preservation; OS, overall survival; DFS, disease-free survival; 5-FU, 5-fluorouracil; CI, continuous intravenous infusion; NR, Not reported; LV, leucovorin.

[a]For the unresectable patients.

[b]For patients receiving curative surgery.

[c]For lower-seated tumors.

250 mg/m$^2$/day of UFUR after RT might be one of the reasons of this satisfactory result. The other assumed reason was a little longer interval of RT-surgery (median 7 weeks) in this series. In a European multicenter randomized trial, a statistically increase in DS was observed for the long-interval group (6–8 weeks) compared to those undergoing surgery within 2 weeks of RT (26% vs. 10%) [30]. A recent retrospective study by Moore et al. also showed a trend toward increased pCR and DS rate with increased interval [31]. Additionally, the SP rate of 55% for lower seated tumors observed in this study were similar to studies using continuous infusion of 5-FU (59–75%) [5,7]. The 3-year overall survival rate of 92% and disease-free survival data of 76% allow this study to be comparable to 5-FU + pre-operative RT [1,7] and higher-dose UFT + pre-operative RT studies [19,20,27].

DS is one of the endpoints of this study. Accurate determination of clinical staging before CCRT is a prerequisite to evaluate DS. The pre-CCRT staging of our cases was based on MRI (65%) and CT scan (35%). MRI is better than CT scan in determining T or N stages, in view of both sensitivity and specificity [32]. Endorectal ultrasonography may have a higher sensitivity for T-stage determination, but the sensitivity for determining the nodal involvement is still poorer than MRI [32]. However, we used CT scan for some of our patients because of its better availability and lower cost.

The high incidence of DS (75%) and pCR (25%) may be the positive factors of the good disease-free survival result. Up to now, none of our patients with pCR had recurrence of disease. Among our limited number of patients receiving curative surgery, those having major DS (pathological T0 and T1) seem to have better disease-free survival than those did not (Fig. 4). Theodoropoulos et al. and Janjan et al. [33,34] also suggested that patients with rectal cancers responding favorably to chemoradiation had better disease-free survival.

We still had four local recurrences in spite of careful RT planning and surgery of curative intent. Three of the local recurrences were clinical T4 and the other was T3 case. This suggests that higher dose (>45 Gy) of pre-operative RT may be needed for locally advanced disease to obtain even better local control. Unilateral inguinal lymph node recurrence was noted in one patient with a tumor 1 cm above the anal verge. We did not irradiate the inguinal area pre-operatively for any case in this study in order to minimize the skin toxicity. In the future, elective irradiation of the inguinal area may be considered for rectal cancer near the anus.

Diarrhea is the most severe adverse event of oral tegafur-uracil/LV/RT for rectal cancer. When UFT (350 mg/m$^2$/day) and LV (15 mg/day) were combined with pre-operative RT, grade 3–4 diarrhea was reported in 43% of the patients [20]. Grade 3–4 diarrhea of 14–23% was reported with UFT at 300 mg/m$^2$/day plus LV and pre-operative RT [19,20]. Recently, another phase II study by Fernandez-Martos et al. showed that the incidence of grade 3–4 diarrhea was 14% when UFT (400 mg/m$^2$/day) alone was used [27]. The incidence of severe diarrhea was diminished by reducing the dose of UFUR (200 mg/m$^2$/day) in this study. Only 9% experienced grade 3–4 diarrhea. This is, by far, one of the lowest rates reported using pre-operative tegafur-uracil/LV/RT in rectal cancer. The absence of grade 3–4 anorexia and nausea, mucositis, or hand foot syndrome is also encouraging. There were also no fatalities due to pre-operative CCRT. By and large, the tegafur-uracil/LV/RT combination was well tolerated in this study. Whether this reduction of severe diarrhea and other toxicities is valid, which needs to be confirmed by future prospective controlled clinical trials.

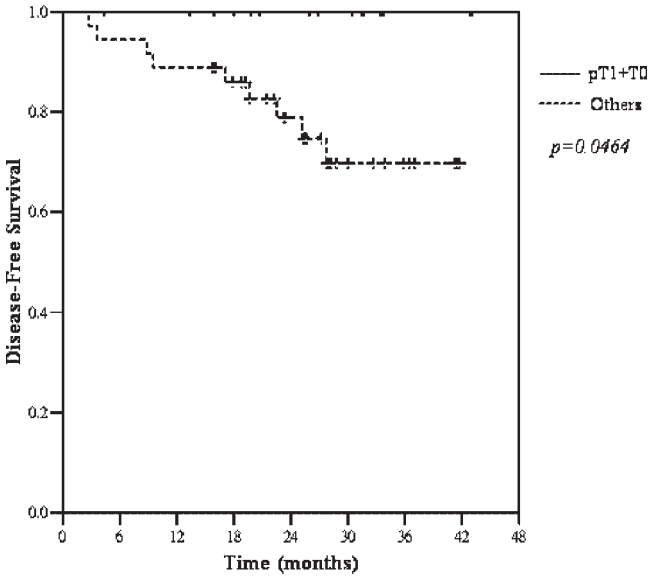


Fig. 4. Disease-free survival of patients with (N = 16) and without (N = 36) major downstaging

One of the major concerns about pre-operative CCRT is its potential adverse late effect after surgery. Although the fraction size used in this study (2.25 Gy) is larger than that of many other studies (1.8 Gy), the incidence of post-operative complications of our study was low and similar to those of others with pre-operative CCRT [35,36]. Some studies also showed that pre-operative irradiation did not result in more post-operative complications than surgery alone [36,37]. Another study in the National Surgical Adjuvant Breast and Bowel Project R03 clinical trial (preliminary results), up to one-third of patients had surgical complications, irrespective of whether they received pre- or post-operative treatment [38]. These results suggested that pre-operative treatment might not increase the surgical complication rate.

## CONCLUSION

Preoperative RT combined with modified dose of oral UFUR and LV is effective in treating rectal cancer patients with tolerable toxicities. It is more convenient to perform than parenteral chemotherapy. Future phase-III clinical trials are necessary.

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# COMMENTARY

Fluorouracil (FU) has been extensively studied since it was first synthesized by Heidelberger and colleagues in 1957 [1]. FU exerts anti-tumor actions through several different mechanisms; inhibition of thymidylate synthase (TS) and RNA synthesis are thought to be the two most important. A metabolite of FU, FdUMP, competitively binds to TS, leading to depletion of intracellular stores of thymidylate. Thymidylate is an essential precursor of thymidine 5′-triphosphate (dTTP), one of the four deoxyribonucleotides required for DNA synthesis. FU also inhibits RNA function through incorporation into RNA in lieu of uracil, leading to perturbation of RNA synthesis and function. Lastly, the FU metabolite FdUTP can interfere with DNA synthesis by incorporation in to DNA.

The synergistic effects of radiation and FU were first investigated by Heidelberger who demonstrated static radiation doses in mice with xenografts became curative when co-administered with FU [2]. The mechanism by which FU leads to radiation sensitization remains unclear; however, S phase cell cycle arrest and inhibition of DNA repair due to depletion of dTTP are hypothesized as playing major roles [3,4].

When FU was first utilized clinically, it was administered intravenously in a bolus fashion due to poor oral bioavailability. Later, it was learned that prolonged exposure to FU leads to increased anti-tumor activity [5]. Despite increased response rates, continuous intravenous infusion (CIVI) FU does not offer a clinically significant survival advantage (11.3 months for bolus vs. 12.1 months for CIVI) [6]. In light of the lack of survival benefit and the cumbersome equipment required for infusional FU, bolus FU continues to be used today. The anti-tumor effect of FU have also been attempted to be modulated utilizing different agents, however leucovorin, which forms a stable complex with FU & TS, is the only agent that continues to be used.

Rich and colleagues were the first to demonstrate the feasibility of protracted infusional FU with radiation [7]. Based upon the results of protracted FU infusion and radiation, orally available FU derivatives have been developed, as oral agents offer convenient route of administration while offering pharmacokinetics mimicking prolonged infusional therapy. Ftorafur (Tegafur) was among the first oral FU derivatives developed. Due to significant CNS toxicity, development in the U.S. was not pursued beyond preliminary trials, albeit it has been approved and used safely for many years in Japan and other countries. Capecitabine is the newest oral FU derivative and has been shown to be as efficacious as bolus 5FU/LV in metastatic CRC as well as adjuvant therapy for CRC [8–10].

The role of tri-modality therapy (surgery, radiation, chemotherapy) in rectal cancer was established by the Gastrointestinal Tumor Study Group (GITSG) Study 7175, which demonstrated a significantly reduced recurrence rate in patients who received chemotherapy and radiation following surgery compared to patients randomized to observation [11]. Subsequently, an Intergroup Rectal Trial published by O'Connell reported CIVI 5-FU during radiation to be better than bolus 5-FU infusion with radiation [12]. Since chemotherapy and radiation clearly decrease recurrent rates in the adjuvant setting, investigators have completed several phase II trials, suggesting induction chemotherapy and radiation could potentially further benefit patients by improving resectability and sphincter preservation, while maintaining the efficacy demonstrated in the adjuvant setting.

Dr. Wang and colleagues report a well-conducted phase II study, investigating the role of pre-operative chemotherapy and radiotherapy with oral tegafur-uracil (UFT) and leucovorin in rectal cancer. Of the 52 patients who received surgery, downstaging was noted in 39 patients (75%), and 13 patients (25%) achieved a pathological complete remission (pCR). Sixteen of 29 patients (55%) with lower-seated tumors, defined at less than 6 cm from anal verge, were able to undergo sphincter

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