

Concomitant administration of uracil-tegafur and leucovorin during adjuvant radiotherapy for locally advanced rectal cancer

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Summary

Purpose: We report the feasibility and toxicity profile, and the impact on local control, disease-free survival and overall survival rates of our study which consisted of post-operative concurrent chemoradiotherapy, followed by adjuvant chemotherapy using uracil-tegafur (UFT)/leucovorin (LV) in locally advanced rectal cancer patients.

Patients and methods: Thirty-one patients operated for rectal adenocarcinoma (pT3/4 or N+) were enrolled onto the study. Twenty-three patients were males and 8 females with median age 62 years (range 21-85). Radiotherapy (RT) to the pelvis with conformal technique and individual blocks was delivered within 8 weeks following surgery. Total RT dose was 50.4 Gy and was given in a conventional single fraction of 1.8 Gy per day. Chemotherapy was administered concomitantly and consisted of UFT (300 mg/m²/day) and LV (30 mg/day) during RT-days. Following chemoradiotherapy, chemotherapy alone was administered for 4 cycles in the same dose for 28 days every 35 days.

Results: No lethal toxicity occurred. All patients com-

pleted the scheduled RT. Concurrent chemotherapy continued in 22 (70.9%) patients until the end of RT. Seventeen (54.8%) patients completed the whole concurrent chemoradiotherapy and adjuvant chemotherapy as planned. No grade 3-4 stomatitis/mucositis or haematological toxicities were observed during the whole treatment period. During concomitant therapy grade 1-2 toxicities were: nausea/vomiting 60%, dyspepsia/gastric pain 39%, diarrhea 39% and dysuria 10%, whereas grade 3 nausea and diarrhea occurred in 6% and 19%, respectively. Median follow-up was 22 months. Two-year local control, disease-free survival and overall survival rates were 96.3%, 72.3% and 83.2%, respectively.

Conclusion: The acute toxicity profile of UFT/LV, local control, disease-free survival and overall survival in the concurrent chemoradiotherapy setting for operated, locally advanced rectal cancer seem comparable with the standard 5-fluorouracil (5-FU)-based therapies.

Key words: concomitant chemoradiotherapy, oral fluoropyrimidine, rectal cancer, survival, toxicity, UFT

Introduction

The primary therapy of rectal cancer is surgery

which can provide satisfactory cure rates in early-stage disease. However, due to the enhanced risk of local recurrence with subsequent decrease in survival, adjuvant chemoradiotherapy is recommended for non-metastatic locally advanced rectal cancer for AJCC stage \geq T3N0M0 or Astler-Coller stage \geq B2 [1-3]. The main component of chemotherapy is 5-FU, generally combined with LV. During irradiation, chemotherapy is given concomitantly for its radiosensitizing effect and is administered either as bolus or as protracted venous infusion (PVI). Some authors have reported that distant metastatic rates were decreased with PVI and improved local and distant control was achieved in the adjuvant setting in patients with rectal cancer [4]. Some studies reported that PVI 5-FU is superior

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to bolus 5-FU with slightly increased response rate probably due to better radiosensitization [5,6]. Although Smalley et al. showed no survival advantage in their study which compared PVI and bolus forms of postoperative adjuvant 5-FU-based chemoradiotherapy, they also reported less toxicity in the PVI arm [7]. Despite promising results, PVI presents some technical disadvantages such as requirement of central venous line, portable pump or hospitalization, and it is perceived as inconvenient by the patients [8].

UFT is an oral fluoropyrimidine composed of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil in a molar ratio of 1:4. Uracil inhibits the dehydropyrimidine dehydrogenase (DPD) and prolongs the half life of tegafur [9]. The role of oral fluoropyrimidines in metastatic colorectal cancer was investigated in two randomized phase III trials. In both trials, toxicity was less than in the standard Mayo Clinic regimen (5-FU plus low dose LV, both given daily for 5 days every 4-5 weeks) with comparable median time to progression [10,11].

Based on this data, we designed the present study of UFT/LV with concurrent RT in locally advanced rectal carcinoma to determine its efficacy and tolerability. In this communication we report the acute toxicity profile with local control, disease-free survival and overall survival rates of this regimen.

Patients and methods

Patient enrolment was done between December 2003 and December 2005 in two radiotherapy centres of Istanbul, Marmara University Hospital and Dr Lutfi Kirdar Kartal Education and Research Hospital.

Eligibility criteria

Patients were eligible for this study if they had histologically proven rectal adenocarcinoma, tumour-negative surgical margins after abdominoperineal (APR) or low anterior resection (LAR) and had locally advanced stage (pT3/4 or N+ and M0) disease. All patients had to be older than 18 years of age, have a performance status (WHO) 0-2 and have not receive prior pelvic RT or chemotherapy. Adequate laboratory values (WBC $\geq 3000/\text{mm}^3$, platelets $\geq 100.000/\text{mm}^3$, AST ≤ 100 IU, ALT ≤ 100 IU, and less than the upper limit of normal of bilirubin and creatinine levels) were also required. Approval by the local ethical committee of both hospitals was required. All patients gave signed informed consent before starting treatment.

Treatment schedule

Adjuvant chemoradiotherapy was started not later than 8 weeks after surgery. RT was given with high energy linear accelerator. The 4-sided (anteroposterior/posteroanterior and 2 lateral fields) box technique was used for the pelvic region in supine position. All fields covered the primary tumor bed, surrounding soft tissues and pelvic lymph nodes. For APR patients the inferior border was enlarged to cover the perineum. The external iliac nodes were included in the RT field in case of pT4 tumors. Computed tomography (CT) simulation and 3D treatment planning were performed to draw target volumes [clinical target volume (CTV) and planning target volume (PTV)]. The fields were treated with 1.8 Gy per fraction to a total dose of 50.4 Gy in 28 fractions. UFT (300 mg/m²/d) and LV (30 mg/d) were given orally 5 days per week during the whole RT period. Adjuvant chemotherapy alone started 4 weeks after the completion of the concurrent therapy. The same chemotherapy doses were given for 28 consecutive days with cycle repetition on the 35th day. Four chemotherapy cycles were planned for all patients. The treatment schema is shown in Figure 1.

During concomitant therapy complete blood count, liver and renal function tests were obtained biweekly. Before each course of adjuvant chemotherapy physical examination and the same biochemical tests were carried out. Disease assessment was done with abdominal and pelvic CT at the beginning of the therapeutic protocol and reassessment was performed at the end of the adjuvant chemotherapy.

Toxicity assessment

Toxicity was graded according to NCI CTC 2.0. If grade 2 side effects from any organ or tissue were observed chemotherapy was stopped until toxicity resolution; during this time RT was continued alone. If grade 3 toxicity occurred, chemotherapy was stopped until the end of RT. During adjuvant chemothera-

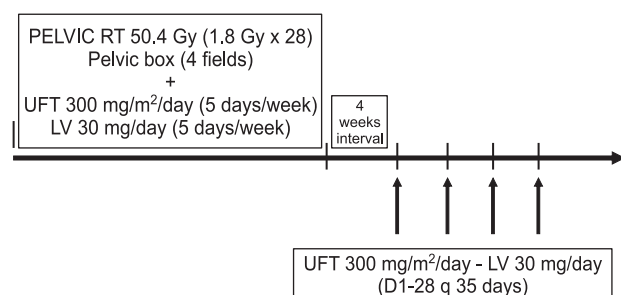


Figure 1. Treatment schema.

py cycles, if grade 3 toxicity was encountered a 20% dose reduction was done.

Survival definitions

Disease-free survival was defined as the time period from the date of surgery to the first appearance of disease relapse or a second primary cancer. Overall survival was defined as the time period starting from the date of surgery to death from any cause.

Statistical considerations

Local control, disease-free survival and overall survival rates were calculated using the Kaplan-Meier product limit method. P-values for toxicity comparisons between concurrent chemoradiotherapy and adjuvant chemotherapy were calculated for each cross-tabulation using χ^2 tests and p-values less than 0.05 were considered statistically significant.

Results

Patient and tumor characteristics

Patient characteristics are shown in Table 1. Thirty-one histologically confirmed rectal adenocarcinoma patients entered the study. Twenty-three (74.1%) patients were males and 8 (25.9%) females. Their median age was 62 years (range 21-83). Surgical procedures were LAR for 16 (51.6%) and APR for 15 (48.4%) patients. All of them had histologically con-

firmed negative surgical margins. Histological grades were as follows: 14 (45.1%) moderately differentiated, 9 (29%) poorly differentiated and 8 (25.8%) unknown differentiation. Lymphatic and vascular invasion was positive in 8 (25.8%) cases.

Exposure to treatment

Two patients withdrew their consent: one during chemoradiotherapy and the other after 2 courses of adjuvant chemotherapy. Their data were included in this analysis.

RT was completed in a median of 7 weeks (range 6-10). All patients completed RT as scheduled. During RT-days concurrent chemotherapy was administered for a median of 6 weeks (range 3-10). Twenty-two (70.9%) patients received more than 90% of the planned chemotherapy dose during RT. Chemotherapy was stopped in 9 (29%) patients because of grade 3 toxicity.

A total of 98 adjuvant post-RT chemotherapy cycles were administered and the median number of cycles per patient was 4 (range 0-4). Twenty-three (74.1%) patients received 4 cycles of adjuvant chemotherapy, while 17 (54.8%) received the whole adjuvant chemoradiotherapy protocol.

Acute toxicity evaluation

Toxicity profiles during treatment are shown in Table 2. No stomatitis/mucositis or grade 3-4 haematological toxicity were observed during both concomitant and post-chemoradiotherapy adjuvant chemotherapy courses. However, gastrointestinal and urinary toxicity were common. Grade 1-2 nausea/vomiting was seen in 54.8% and grade 3 in 6.4% of the patients. Grade 1-2 diarrhea was encountered in 45%, and grade 3 in 19.3% of the patients during concurrent therapy. Other clinical adverse events included dyspepsia (grade 1-2, 38.7% and grade 3, 3.2%), proctitis (grade 1-2, 9.6%), and urinary symptoms (grade 1-2, 29%, grade 3, 6.4%). Grade 1-2 diarrhea was 16.1% during adjuvant chemotherapy courses, whereas 6 (19.3%) patients developed grade 3 toxicity (3 diarrhea and 3 nausea/vomiting); the UFT dose was reduced in those patients according to the protocol. The volume of RT field according to the surgical procedure (APR vs. LAR) had no impact on side effects intensity during concurrent treatment.

Disease-free and overall survival

The patients' median follow up was 22 months (range 4-35). Two patients were lost to follow-up. A

Table 1. Patient characteristics

| Characteristic | Patients | |
|--|------------|------|
| | n | % |
| Age, years median (range) | 62 (21-85) | |
| Sex | | |
| Male | 23 | 74.1 |
| Female | 8 | 28.8 |
| Type of resection | | |
| Low anterior | 16 | 51.6 |
| Abdomino-perineal | 15 | 48.3 |
| Stage | | |
| T ₃ N _x M ₀ | 1 | 3.2 |
| T ₃ N ₀ M ₀ (Astler-Coller B ₂) | 12 | 38.7 |
| T ₂ N ₁₋₂ M ₀ (Astler-Coller C ₁) | 2 | 6.4 |
| T ₃ N ₁₋₂ M ₀ (Astler-Coller C ₂) | 12 | 38.7 |
| T ₄ N ₁₋₂ M ₀ (Astler-Coller C ₃) | 4 | 12.9 |
| Grade | | |
| Moderate | 14 | 45.1 |
| Poor | 9 | 29 |
| Unknown | 8 | 25.8 |

Table 2. Toxicity according to the kind of treatment

| Toxicity | Grade | Concurrent CRT n (%) | Adjuvant CT n (%) | p-value |
|-------------------------|-------|-------------------------|----------------------|---------|
| Gastrointestinal | | | | |
| Diarrhea | 1 | 3 (10) | 3 (10) | 0.041 |
| | 2 | 9 (29) | 2 (6) | |
| | 3 | 6 (19) | 3 (10) | |
| Proctitis | 1 | 2 (6) | – | NS |
| Dyspepsia/gastric pain | 1 | 8 (26) | 4 (13) | NS |
| | 2 | 4 (13) | 1 (3) | |
| | 3 | 1 (3) | – | |
| Nausea/vomiting | 1 | 11 (35) | 6 (19) | 0.003 |
| | 2 | 8 (25) | – | |
| | 3 | 2 (6) | 4 (13) | |
| Genitourinary | | | | |
| Dysuria | 1 | 1 (3) | 3 (10) | 0.021 |
| | 2 | 6 (19) | – | |
| | 3 | 2 (6) | – | |
| Pollakiuria | 1 | 1 (3) | 1 (3) | NS |
| | 2 | 7 (22) | 3 (10) | |
| | 3 | – | 1 (3) | |
| Dermatitis | 1 | 3 (10) | 1 (3) | NS |

CRT: chemoradiotherapy, CT: chemotherapy, NS: non significant

total of 5 (16%) patients relapsed: 2 with both local recurrence and distant metastases and 3 with distant metastases alone. One of the local recurrences occurred 11 months following LAR and the patient was re-operated (APR) at the time of relapse. Two patients developed lung, 2 liver and 1 solitary bone metastases. All these metastases were confirmed with appropriate imaging studies (CT scan, MRI, or bone scan). First-line systemic chemotherapy was started for all patients with relapse and RT was given for palliation of bone metastases.

Five (16%) patients died. One of disease progression in the liver. There were 2 patients older than 80 years who died due to acute myocardial infarction at the 9th and 19th month of follow-up without evidence of disease recurrence. One patient died of acute abdomen possibly attributable to septic shock secondary to acute intestinal obstruction due to postoperative benign adhesions at the 12th month of follow-up. One patient died of unknown cause in another hospital 13 months after completion of the last cycle of post-concomitant chemotherapy.

At the time of analysis 2-year local control, disease-free and overall survival rates were 96.3%, 72.3% and 83.2%, respectively (Figures 2 and 3).

Discussion

Adjuvant 5-FU-based chemoradiotherapy has been considered standard therapy in transmural or

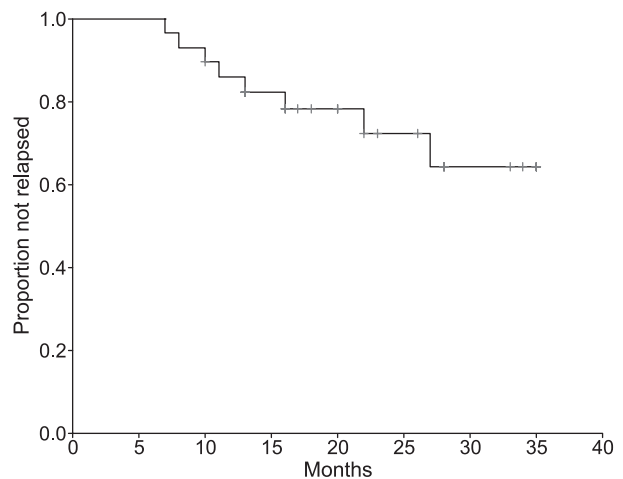


Figure 2. Kaplan-Meier curve: disease-free survival.

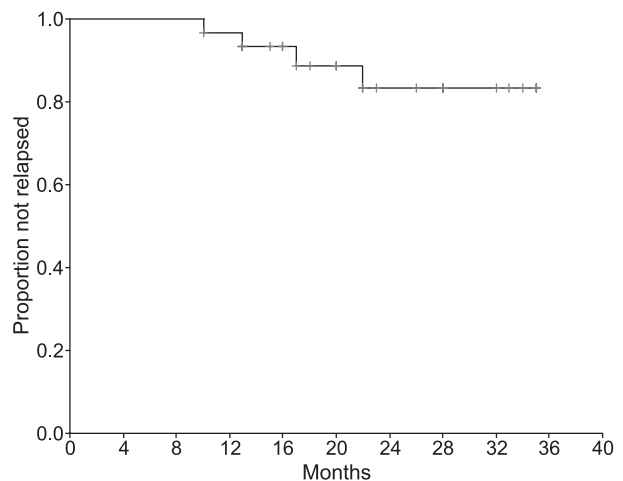


Figure 3. Kaplan-Meier curve: overall survival.

node-positive rectal cancer patients and it can be administered as either PVI or bolus [1-4]. During RT, continuous 5-FU infusion is more effective than bolus injection. Recent data showed that the incidence of gastrointestinal side effects are similar in PVI and bolus groups but grade 3 and 4 haematological toxicity is significantly less in PVI administration (4% vs. 55%) [7]. Despite that, PVI has disadvantages like infusion pump and catheter requirement and increased related complications, like infections [4]. Therefore, more preferable routes, like oral administration, are currently being tested, especially in the preoperative setting with concurrent RT [12-14].

Oral fluoropyrimidines provide a home-based therapy and patients prefer this kind of treatment for its convenience, shortening of hospital stay and stress, less side effects which allow to maintain a normal lifestyle during treatment but the question is whether they have an equal efficacy and less toxicity [15]. Hence, in our study the focus of interest was UFT, a combination of uracil and tegafur, which achieves similar concentrations of 5-FU when administered in continuous infusion [16]. In preliminary studies UFT has shown an adequate serum and also intratumoral drug concentration during weekday-on with RT [17].

Data from large randomized trials showed that UFT/LV in previously untreated metastatic colorectal carcinoma patients produce equivalent survival compared with PVI 5-FU-based regimens [9,10]. UFT/LV has not only the advantage of oral administration but also has less toxicity. Douillard et al. reported that their UFT/LV arm had significantly less severe side effects like haematological (leukopenia 1% vs. 19%, neutropenia 1% vs. 56%) or gastrointestinal (stomatitis/mucositis 1% vs. 21%) toxicity. However, diarrhea (21% vs. 16%) and nausea/vomiting (13% vs. 10%) were slightly higher in the UFT/LV arm, but these differences were not significant [10].

In a prospective study exploring the timing of RT it was suggested that early concurrent therapy following surgery improves disease-free survival compared with the standard regimen which consisted of 2 cycles of chemotherapy prior to concurrent chemoradiotherapy [18]. Therefore, we decided to start with concurrent chemoradiotherapy following surgery and then to continue with chemotherapy alone.

No consensus exists on the optimal LV dose. In preoperative concomitant studies LV dose ranged between 0 and 90 mg/day [12-14,19]. Although Hoff et al. in their phase I study recommended as maximum tolerated dose of UFT 350 mg/m² and LV 90 mg/day, we preferred to give UFT 300 mg/m² and LV 30 mg/day according to the de la Torre et al. phase II study

[13, 20]. In the latter trial grade 3 diarrhea was 23% while in our study it was only 19%. These results are quite similar, however we administered 50.4 Gy in the postoperative setting while the others were preoperative studies.

O'Connell et al. showed in their study that severe or life-threatening acute diarrhea was observed in 24% of patients in the PVI 5-FU arm whilst it was 14% in the bolus 5-FU arm. However, grade 3 nausea/vomiting in our study was encountered in 6.4% of the cases, which was higher than other PVI 5-FU studies [4]. In another study with concurrent administration of RT with UFT 19% of the patients had grade 3-4 diarrhea which is very similar to our results [21]. Feliu et al. studied two different doses of UFT (350 mg/m² and 300 mg/m²) and they observed severe diarrhea in 21% and 14% of the patients, respectively [19]. In our study, severe diarrhea was 19.3% and this result is comparable with previous reports.

Pfeiffer et al. tested UFT with high dose RT (60 Gy) as preoperative concurrent treatment. They administered UFT in a dose range between 150 and 300 mg/m² and gave LV in a flat dose of 22.5 mg/day during weekdays [14].

It is well-known that the most important outcome prognosticator following resection of colorectal cancer is the pathologic stage at presentation. The outcomes of patients treated with postoperative chemoradiotherapy are different in several relevant studies.

In the National Cancer DataBase Report [22], 5-year overall survival rate in patients with stage II rectal cancer treated with surgery alone or surgery combined with RT was 55% (reported as a combined group), whilst patients treated with a combination of surgery, RT, and chemotherapy or surgery and chemotherapy was 61.5%. The 5-year survival for patients with stage III disease treated with multimodal therapy was 41.5% in this report.

In a large study comparing preoperative vs. postoperative chemoradiotherapy for rectal cancer local relapse rate, the cumulative incidence of distant recurrence, and overall survival rates for the arm treated with postoperative chemoradiotherapy were 13%, 38%, and 74%, respectively [21]. Although the median follow up in our study is relatively short local control, disease-free survival and overall survival rates are 96.3%, 72.3% and 83.2%, respectively.

In the present study concurrent chemoradiotherapy was administered to 22 (70.9%) patients till the end of RT and the most common reason for permanent therapy interruption was diarrhea. During the protocol no stomatitis/mucositis, leukopenia, thrombocytopenia or life-threatening toxicity were observed.

Although we did not compare directly two different regimens, our results imply that the toxicity of RT combined with UFT/LV was comparable with concurrent treatments with PVI or bolus 5-FU. We believe that further studies with larger patient groups and longer follow up are needed to explore the side effect profiles and efficacy of this new regimen in advanced-stage rectal cancer.

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