Hiroshima J. Med. Sci.
Vol. 54, No. 3, 87~91, September, 2005
HIJM 54–15

Neoadjuvant Therapy of Rectal Cancer using Oral Tegaful-Uracil (UFT) plus Concomitant Radiotherapy —A case report—

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ABSTRACT

A 59-year-old male patient with rectal cancer 2 cm in diameter (T2) at the peritoneal reflection with suspicious left lateral node metastasis was treated with 400 mg of preoperative oral uracil and tegaful (UFT) for 5 weeks, 5 days a week in combination with concomitant radiotherapy of 45 Gy per 25 fractions for 5 weeks. After resting for another 5 weeks, colon fiberscopy, barium enema, and computed tomography revealed a trace of the primary tumor and a 40% shrinkage of the lateral metastasis. The serum CEA level decreased to the normal range during treatment. The adverse effects were nausea, bloody stool and elevation of transaminase, all at grade 1. Low anterior resection with a left hemi-lateral lymphadenectomy was performed through a suprapubic, one hand-size incision without laparoscopy. The preoperative treatment did not affect any operative procedures, and no postoperative complications occurred. The surgical specimen showed that the rectal tumor had been remarkably shrunk by the preoperative treatment, to the level of a superficial type tumor. Histological analysis indicated moderately differentiated adenocarcinoma cells that were present at only 2 mm in diameter in the mucosal layer, 6 mm in the submucosal layer, and 1 mm or less in the muscular layer with scar formation. No metastasis was detected in the 16 lymph nodes dissected, but an organizing tumor thrombus, which had preoperatively been diagnosed as lateral node metastasis, was detected. These results suggest that preoperative oral UFT plus concomitant radiotherapy may be a feasible, tolerable and effective treatment for patients with rectal cancer.

Key words: *Neoadjuvant, UFT, Radiation, Rectal cancer, One hand-size incision surgery (OHaSIS)*

Rectal adenocarcinoma has a very high rate of local relapse with surgery alone. Therefore, perioperative adjuvant radiotherapy with or without chemotherapy has been studied worldwide. In the United States, two important phase III clinical trials have shown the benefit in the local control and distant failure rates when radiation is postoperatively combined with 5-fluorouracil (5FU)-based chemotherapy. The Gastrointestinal Tumor Study Group clinical trial[4] demonstrated a reduction in the number of local failures with a significant benefit in the seven-year survival in patients treated with surgery and postoperative chemoradiation as compared with those treated with surgery alone. The North Central Cancer Treatment Group clinical trial[5] also showed an improved rate of pelvic failure patients postoperatively treated with chemoradiation along with a survival benefit. These findings led the National Cancer Institute Consensus Conference in 1990[7] to recommend postoperative adjuvant treatment with radiation and chemotherapy for all patients with Dukes B2 and C disease.

Compared with postoperative radiochemotherapy, however, preoperative chemotherapy plus radiotherapy offers some advantages over adjuvant therapy for patients with middle to lower rectal cancer: 1) micrometastasis is treated early in the course of the disease, 2) the risk of tumor seeding during surgery is reduced, 3) RT toxicity is also reduced, 4) the efficacy of chemotherapy and radiotherapy is higher in a tumor with an intact vasculature, 5) if the tumor shrinks, a sphincter-preserving procedure can be performed[2]. In the 1990s, preoperative chemoradiotherapy was studied for patients with rectal cancer. Although the

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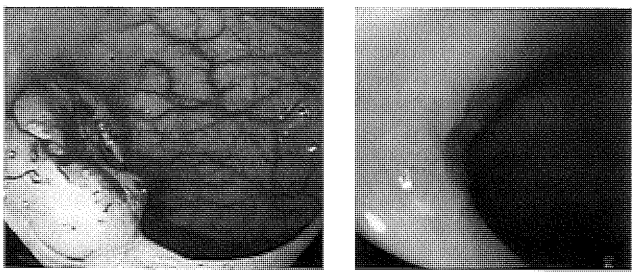
optimal schedule of 5FU-based preoperative chemotherapy has not been defined, the continuous infusion of 5FU has the advantage of achieving a constant level of radio-sensitizing drugs during the radiation course. This regimen has been shown to be well tolerated and results in the downstaging of a large percentage of rectal cancers[8,9]. However, the need for prolonged venous access, which requires either hospitalization or the use of an ambulatory infusion pump, both of which increase the cost of treatment, can limit the use of continuous 5FU schemes.

Oral fluoropyrimidines constitute an alternative to 5FU. UFT is one of the oral formulations of the fluoropyrimidines that combines uracil and tegafur in a fixed molar ration of 4:1. The pharmacokinetic profile of UFT is similar to that of continuous-infusion 5FU[6]. Fernandez-Martos et al[3] have studied preoperative UFT plus concomitant radiotherapy for patients with operative rectal cancer. They reported that the downstaging rate was 54%, the pathologic complete response (pCR), in which cellular viability criteria are taken into account, was 15%, and a sphincter-preserving operation was possible for 25% of the patients who otherwise would receive Miles' operation. In addition, a significant higher survival and recurrence-free survival rate was evident in patients for whom downstaging occurred. Because of this observation, we introduced preoperative UFT plus concomitant radiotherapy for a rectal cancer patient with T2 and N2 lateral lymph node metastasis. In this paper, we present the treatment schedule and excellent tumor responses.

CASE PRESENTATION

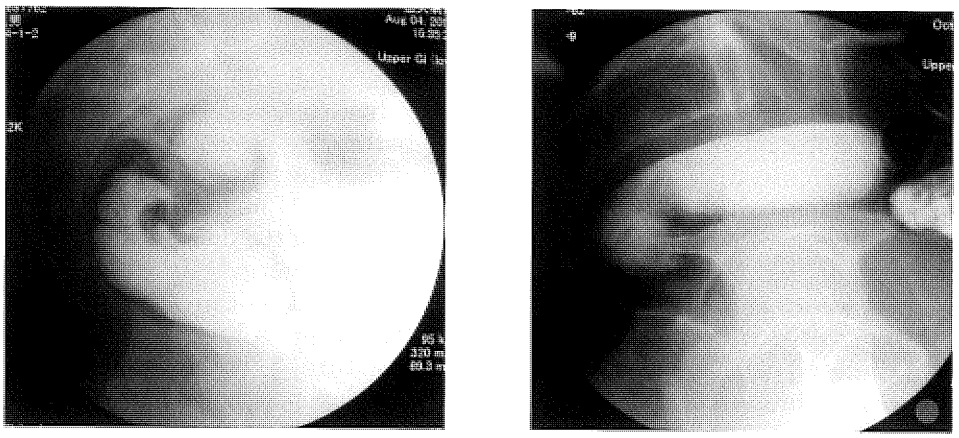
A 59-year-old male patient (165 cm in height, 65 kg in weight) with a complaint of bloody stools, appeared to our hospital. A colon fiberscopy revealed a rectal cancer 2 cm in diameter at the peritoneal reflection (Fig. 1a). A well- to moderately-differentiated adenocarcinoma was defined by microscope in the biopsied samples. A barium enema confirmed the tumor location at the peritoneal reflection (Fig. 2a). Computed tomography (CT) showed a rectal tumor that was located at the left anterolateral wall and had invaded the muscular layer (Fig. 3a). No liver and lung metastasis was evident. Left lateral node metastases were strongly suspected along with one in the left internal iliac artery (Fig. 3b). Collectively, we diagnosed rectal cancer with T2N2M0.

After obtaining written informed consent, preoperative chemoradiotherapy was scheduled (Fig. 4). UFT (400 mg/body/day) was administered orally for 5 consecutive days a week for 5 weeks. Radiotherapy, at a fraction of 1.8 Gy a day, was concomitantly performed over the UFT for 5 consecutive days a week for 5 weeks, culminating in a total dose of 45 Gy. The adverse effects observed were nausea, bloody stool and the elevation of transaminase, all at grade 1 (Table 1). The patient was allowed to rest for the next 5 weeks, and the tumor responses were then evaluated. The colon



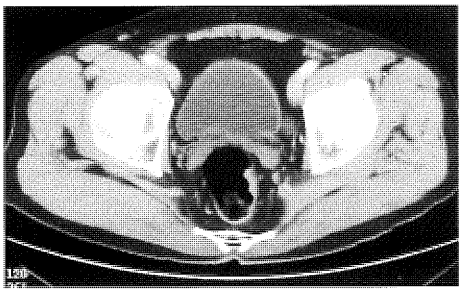
(a) (b)

Fig. 1. Colon fiberscopy before and after preoperative UFT plus radiotherapy
Preoperative UFT plus concomitant radiotherapy was administered for 5 weeks, and colon fiberscopic examination was performed after another 5-week rest, just before surgery. Findings before (a) and after (b) the treatment are shown.



(a) (b)

Fig. 2. Barium enema before and after preoperative UFT plus radiotherapy
Preoperative UFT plus concomitant radiotherapy was administered for 5 weeks, and a barium enema was performed after another 5-week rest, just before surgery. Findings before (a) and after (b) the treatment are shown.



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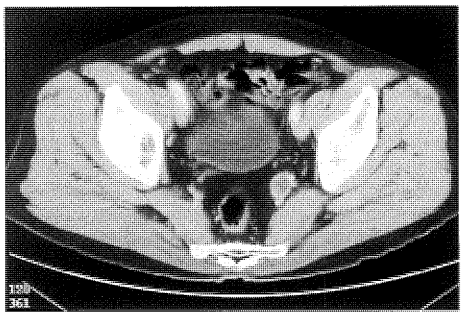

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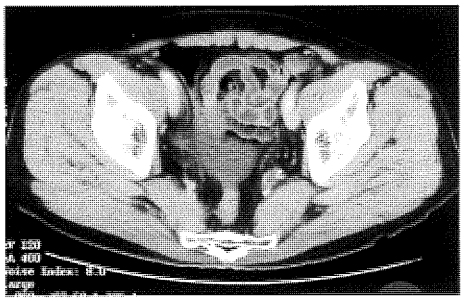


(c)

Fig. 3. Computed tomography before and after preoperative UFT plus radiotherapy
Preoperative UFT plus concomitant radiotherapy was administered for 5 weeks, and computed tomography was performed after another 5-week rest, just before surgery. Findings of the primary tumor (a) and lateral metastasis (b) before the treatment, and lateral metastasis after the treatment (c) are shown.

fiberscopy and barium enema showed marked tumor shrinkage (Fig. 1b, 2b). A CT scan revealed 40% shrinkage of the lateral lymph node metastasis (Fig. 3c). The serum CEA level dropped into the normal range during the preoperative treatment (Table 1). A low anterior resection with lateral node dissection was then performed under a suprapubic one hand-size incision[12]. The preoperative treatment did not affect any surgical procedures.

The surgical specimen showed that the irradiated rectal mucosa of the whitened area (left side of the specimen) was distinguishable from the non-irradiated area (right side of the specimen), and that the rectal tumor had shrunk remarkably compared to its size before treatment (Fig. 5a), to the level of a superficial type (Fig. 5b). The surgical margin at the anal side of the tumor was 2.5 cm (Fig. 5a). Histological analysis indicated that moderately-differentiated adenocarcinoma cells 2 mm in diameter were present in the mucosal layer, 6 mm in the submucosal layer and 1 mm or less in the muscular layer, with scar formation (Fig. 6a, b). No metastasis was detected in the 16 lymph nodes dissected, although an organizing tumor thrombus, which had preoperatively been diagnosed as lateral lymph node metastasis, was histologically pointed out (Fig. 6c).

The postoperative course went quite well. Liquid meals were begun on the 3rd postoperative day, and hospitalization was terminated on the 9th postoperative day. As adjuvant chemotherapy, 300 mg/body/day UFT will be administered for 2 years. A CT scan at the 3rd postoperative month showed no local or distant metastases.

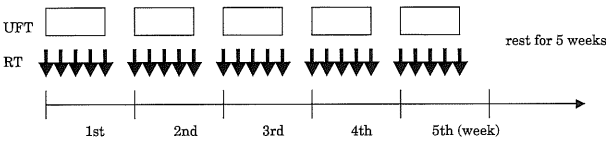
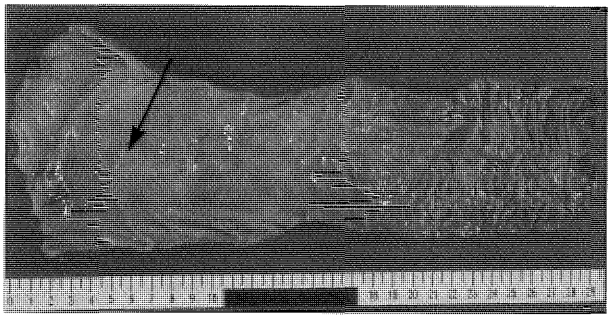


Fig. 4. Schedule of preoperative UFT plus radiotherapy
UFT (400 mg/body/day) was administered orally in combination with concomitant radiotherapy (1.8 Gy per fraction, 25 fractions) for 5 consecutive days a week for 5 weeks. After another 5-week rest, surgery was performed.

Table 1. Hemato-chemistric effects of preoperative UFT plus radiotherapy

Measures	pre-treatment	after treatment	before operation
WBC (/μl)	6870	4410	4210
Hg (g/dl)	14.2	13.0	13.4
Platelets (x10^4/μl)	20.8	15.4	20.3
GOT (IU/L)	16	24	27
GPT (IU/L)	25	56*	37
BUN (mg/dl)	20	16	15
Creatinin (mg/dl)	1.04	1.00	1.05
CEA (ng/ml)	7.5*	5.3	3.2

Preoperative UFT plus concomitant radiotherapy was administered for 5 weeks. A hemato-chemistric examination was performed before and after the treatment, and just before the surgery. Asterisk indicates abnormal values.



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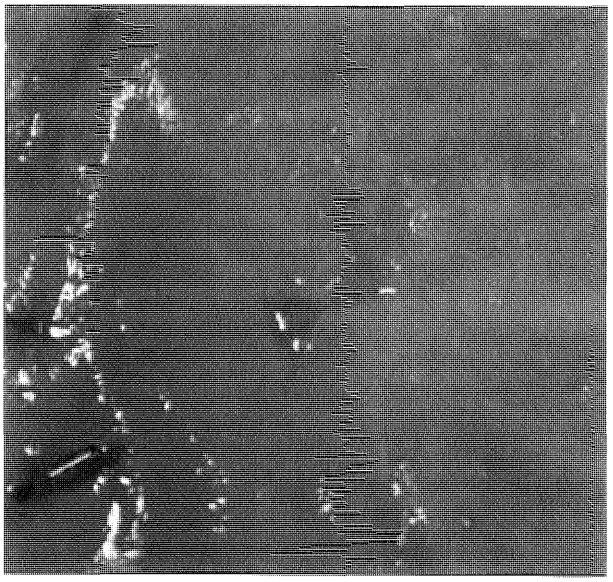
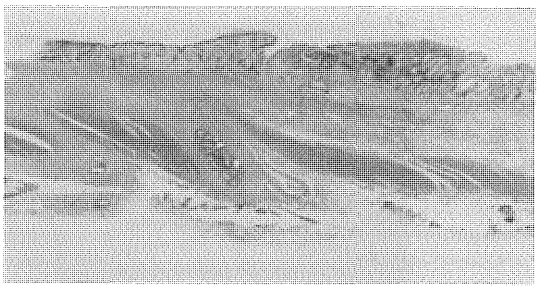


(b)

Fig. 5. Surgical specimen of low anterior resection after preoperative UFT plus radiotherapy
Preoperative UFT plus concomitant radiotherapy was administered for 5 weeks, and low anterior resection was performed after another 5-week rest. A formaldehyde-fixed surgical specimen is shown. (a), Mucosal view of the whole specimen. Whitened mucosa is observed at the distal (left) side of the specimen, which is just at the irradiated area of the rectum. Arrow indicates the shrunken tumor. Two clips, which were endoscopically marked preoperatively at the 2 cm-anal side of the tumor, can be seen. (b), Close-up of the tumor.

DISCUSSION

In this paper, we presented a case for whom preoperative oral UFT administered concomitantly with radiotherapy was highly effective. As for the dose of UFT, Sadahiro et al[10] have reported that 400 mg/m^2 UFT administration for 5 days a week for 2 weeks in combination with concomitant radiotherapy of 20 Gy per 10 fractions plus 15 Gy of intra-operative radiotherapy was feasible for treating patients with rectal cancer, and showed no grade 3, 4 toxicity. However, Fernandez-Martos et al[3] demonstrated that 400 mg/m^2 UFT administration for 5 days a week for 5 weeks in combination with concomitant radiotherapy of 45 Gy per 25 fractions resulted in adverse effects in 16% of



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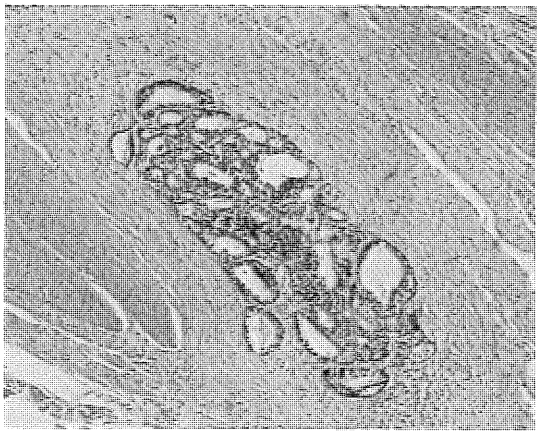

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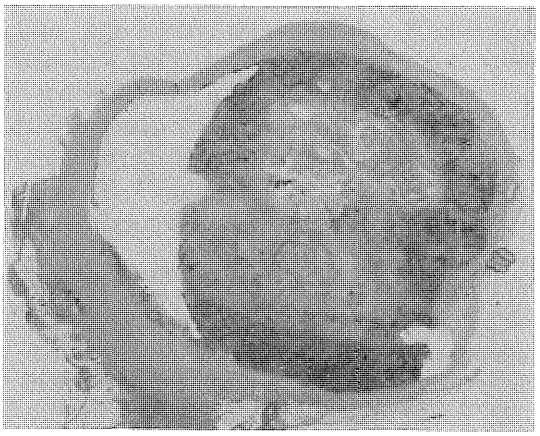

(c)

Fig. 6. Histopathological findings of the tumor
Hematoxylin and eosin staining was performed. (a), Cancer cells were seen 2 mm in diameter in the mucosal layer, 6 mm in the submucosal layer and 1 mm or less in the muscular layer, with scar formation. (b), Moderately-differentiated adenocarcinoma cells in the muscular layer with scar formation, close-up. (c), Lateral metastasis. This does not have a lymph node structure, but shows tumor cells in vasculature.

the patients enrolled, and thus a reduction in the dose of UFT was needed. This difference in the adverse effects may be explained by the difference in the dose of the radiotherapy administered concomitantly with UFT. Therefore, we chose a reduced dose of 400 mg/body/day of UFT in combination with a concomitant 45 Gy radiation per 25

fractions.

In our experience, the schedule of oral UFT administration for 5 days a week with a rest period of 2 days appeared to result in good compliance and safety, and was, most importantly, effective. Sadahiro et al[11] have demonstrated that UFT administration for 5 days a week with a rest period of 2 days achieved comparatively highly sustained 5FU levels within the tumors, even during the two-day rest period. More recently, it was reported that adjuvant oral UFT, which was administered for 5 days a week with a rest period of 2 days for 1 year, improved survival for patients with pathologic TNM stage III rectal cancer[1]. Thus, this schedule of weekday-on/weekend-off for oral UFT administration may be a standard regimen for treating patients with rectal cancer.

The interval from the completion of preoperative chemoradiotherapy to surgery has not been established. It has been described as 4 to 6 weeks[3,6,8]. In our case, a 5-week interval was found to be acceptable to our patient, and helped make the operation bearable. No effects from the preoperative chemoradiotherapy were observed during the operation, although the radiotherapy certainly damaged the rectal mucosa, as shown in the mucosal color of the resected specimen. We therefore agree that the interval from the completion of preoperative chemoradiotherapy to surgery should be 4 to 6 weeks.

As for survival, Fernandez-Martos et al[3] have described that the rate of recurrence-free survival (RFS) at 3 years was 92% for patients with downstaging and 51% for those who had not responded to the preoperative UFT plus concomitant radiotherapy. Our patient showed a marked tumor response to the preoperative UFT plus concomitant radiotherapy, which would indicate a possible long RFS period. However, in this patient tumor thrombus was present in the branch of the left internal iliac vein, suggesting a poor prognosis and a need of closer follow-up for possible distant metastases.

(Received July 6, 2005)
(Accepted July 27, 2005)

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