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Oral UFT (uracil plus futrafur) for neoadjuvant chemotherapy of gastric cancer

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Abstract:
Background. **Neoadjuvant chemotherapy has become one of the topics of interest in chemotherapy of gastric cancer; the present study assessed the clinical benefits of neoadjuvant chemotherapy with oral uracil and futrafur (UFT) for gastric cancer.**
Methods. **Between 1991 and 1997, 82 patients with gastric cancer (36 with early and 46 with advanced cancers) received UFT at 300–600 mg/day orally for 1–6 weeks before surgery. Objective responses, histological effects, and postsurgical survival rates were assessed.**
Results. **In 69 of the 82 patients, the objective responses of the primary lesions were assessed by endoscopy or upper gastrointestinal series examination, and 2 complete responses (CR)s, 25 partial responses (PRs), and 42 no changes (NCs) were seen (39.1% response). Histological effects were evaluated in 82 patients, and 2 grade 3, 11 grade 2, 11 grade 1b, 27 grade 1a, and 31 grade 0 effects were seen. A longer period of UFT administration was associated with a CR or PR. However, the objective responses did not correlate with the histological effects. All the patients underwent gastrectomy, and during the median follow-up period of 41 months, 3-year survival rates were 97.1% for pTNM stage 1, 75% for stage 2, 86.7% for stage 3, and 41.6% for stage 4. The survival rates of stage 3 and stage 4 patients were higher than those of the historical controls in our department. However, CR or PR did not correlate with the improvement in survival. Side effects before surgery were not serious; they included slight myelotoxicity, liver dysfunction, and anorexia; however, 3 patients (3.7%) had suture insufficiency, 3 patients (3.7%) had methicillin-resistant *Staphylococcus aureus* (MRSA) enteritis, and 7 patients (8.5%) had liver dysfunction.**
Conclusions. **Preoperative chemotherapy for gastric cancer with oral UFT was safe and resulted in a good local response (macro- and microscopically) which may indicate the possibility of improved survival with neoadjuvant chemotherapy with UFT. Furthermore, preoperative chemotherapy with oral UFT is easy and patients can receive this treatment on an outpatient basis.**

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Key words: gastric cancer, neoadjuvant chemotherapy, UFT

Introduction

Although the results of treatment for gastric cancer in Japan have been improving over the past two decades, gastric cancer is still one of the leading causes of cancer death in Japan. The 5-year survival rates of gastric cancer patients after gastrectomy have reached more than 90% for stage 1 and 70%–80% for stage 2. However, the prognosis of patients with stage 3 or 4 gastric cancer is still poor, and 5-year survival rates are about 40% for stage 3 and 5%–10% for stage 4. In order to improve the treatment results for gastric cancer, a variety of therapies have been employed, and chemotherapy has played the most important role. However, it is still unclear whether postoperative adjuvant chemotherapy improves survival, although gastric cancer is now considered to be relatively sensitive to chemotherapy compared with cancers of other digestive organs.

Since the introduction of cisplatin (CDDP), a variety of combination chemotherapies, including etoposide + 5-fluorouracil (5FU) + CDDP (EAP) and 5FU + Adriamycin + CDDP (FAP) regimens have been employed for the treatment of gastric cancer [1–4]. After the report by Wilke and colleagues (5), neoadjuvant chemotherapy has become one of the topics of interest in chemotherapy of gastric cancer [5–7]. The first reports on neoadjuvant chemotherapy of gastric cancer were published in Japan, in the 1960s [8,9], and since these reports, many Japanese researchers have employed various neoadjuvant chemotherapies [10–17]. The major purpose of neoadjuvant chemotherapy is preoperative downstaging, to enable more curative surgery. Previous neoadjuvant chemotherapies employed intensive chemotherapies such as EAP or FAP, and we

have also employed an intensive 5FU + CDDP + 4′-epirubicin (FPEPIR) regimen (a modified version of the FAP regimen) [18,19]; however, these therapies frequently cause serious side effects and result in the interruption or postponement of surgery; their true effects are still unclear.

In Japan, neoadjuvant chemotherapy regimens have been different from those used in Western countries, because many neoadjuvant regimens have included oral 5-FU or a mixture of uracil and futrafur at 4:1 (UFT) [12,13,16,17]. In general, the choice of adjuvant chemotherapy for gastric cancer in Japan has differed from that in the United States and European countries; in Japan, oral chemotherapy with fluoropyrimidines has been the standard regimen for gastric cancer. Among these oral fluoropyrimidines, UFT is the most popular agent in Japan. The side effects of oral UFT are not serious; accordingly, UFT is used especially for adjuvant chemotherapy after surgery on an outpatient basis in Japan [20–22]. The response rates of digestive organ cancers to UFT alone in Japan were reported to be: gastric cancer, 27.7%; colorectal cancer, 25.0%; liver cancer, 19.2%; pancreatic cancer, 25.0%; and gallbladder or bile duct cancer, 25.0% [23]. These results are similar to those of intensive intravenous chemotherapies. Accordingly, UFT can be employed for neoadjuvant chemotherapy instead of these intensive chemotherapies, and neoadjuvant chemotherapy with oral UFT may have a major advantage, in that UFT can be administered on an outpatient basis. To achieve downstaging during the waiting period for surgery, we have employed preoperative chemotherapy with oral UFT from 1991, and a total of 82 patients have received this therapy. In the present study, the clinical benefits of preoperative chemotherapy with oral UFT for gastric cancer during the waiting period for surgery were assessed with regard to the objective response and the benefits in terms of postsurgical survival.

Patients and methods

Patients

Two basic criteria for preoperative chemotherapy with UFT had to be met before administration: (1) histological or cytological proof of gastric cancer, and (2) performance status ≤ 3 on the European Cooperative Oncology Group (ECOG) scale. Contraindications included: (1) total disability (performance status [PS] = 4, ECOG score), (2) prior chemotherapy, radiotherapy, or immunotherapy within 4 weeks, (3) active infectious disease, (4) severe anemia (hemoglobin < 9.0 g/dl), leukopenia (<3000 white blood cells/mm^3), thrombocytopenia (<70 000 platelets/mm^3), azotemia (creatinine > 2.0 mg/dl), or liver dysfunction (GOT, GPT, and alkaline phosphatase > four fold normal limits), (5) severe heart disease or concomitant malignant disease, and (6) pregnancy. All patients and their families were fully informed with regard to the treatment program, and informed consent was obtained.

Table 1. Patient profile

Number of patients		82
Age (years)		31–86 (average, 65.7 ± 9.6)
Sex		Male:female = 56:26
Macroscopic diagnosis before surgery		
1. Early cancer:		$n = 32$
Type	I	$n = 4$
	IIa	$n = 4$
	IIb	$n = 0$
	IIc	$n = 23$
	IIa + IIc	$n = 2$
	III	$n = 2$
2. Advanced cancer:		$n = 50$
Borrmann	I	$n = 4$[a]
	II	$n = 8$
	III	$n = 30$
	IV	$n = 8$
Postoperative pTNM stage classification (UICC, 1987)[b]		
Stage	1	$n = 40$
	2	$n = 6$
	3	$n = 19$
	4	$n = 17$

[a] Including one recurrent cancer of the remnant stomach
[b] Excluding one recurrent cancer of the remnant stomach

Between 1991 and 1997, a total of 82 patients with gastric cancer were included in the present study: 36 with early (pT1) gastric cancers and 46 with (pT2–4) advanced gastric cancer according to the postoperative International Union against Cancer classification. After surgery, the stage of gastric cancer was classified according to the (UICC) TNM stage classification (1987). The patient profile is summarized in Table 1.

Treatment protocol for neoadjuvant chemotherapy with UFT

The patients were administered UFT orally after meals during the waiting period for surgery. The administration usually started from the first visiting day to the outpatient ward and the patients were given the last UFT at 6 p.m. on the day before surgery. One capsule of UFT includes 100 mg of futrafur (FT), and the dose of UFT is usually expressed as the does of FT. Three different doses (300, 400, and 600 mg/day) were used, and the dose of UFT for each patient was determined according to the patients condition (PS, body weight, age, hematology, and serum biochemistry), because UFT sometimes causes serious myelotoxicity or hepatotoxicity.

Examinations of hematology, serum biochemistry, and serum tumor markers, and evaluations of the symptomatic status and performance status were routinely performed at weekly or biweekly intervals, sometimes more frequently. The size of the primary lesion was usually assessed before UFT administration and 1 or 2 days before surgery by endoscopy and/or upper gastrointestinal series examination, sometimes more frequently. If the disease appeared to progress or serious side effects were seen, the patients were either managed symptomatically and supportively or offered alternative experimental regimens if their general condition seemed to be appropriate.

Postsurgical adjuvant chemotherapy

The patients were treated with adjuvant chemotherapy according to their postsurgical stage classification. Stage 1–3 patients received adjuvant chemotherapy with UFT for 1–3 years and stage 4 patients received intensive chemotherapy with one to four courses of CDDP, 5-FU, and epirubicin (FPEPIR regimen) [19] according to their condition and then received oral UFT daily for as long as possible.

Evaluation of objective response and histopathological effects

The objective response was evaluated as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD) by endoscopy, upper gastrointestinal series examination, and computed tomography (CT) scan, and the histopathological effect was evaluated based on the grade (0–3), according to the criteria of the Japanese Research Society for Gastric Cancer (1995, First English Edition). The duration of the response was not included in the evaluation of the objective response, because all patients underwent surgery.

Evaluation of side effects

The WHO standard criteria for toxicity [24] were used.

Follow-up of patients

All patients were followed-up by physical examination, general X-ray examination, ultrasonography (US), CT, routine hematologic and biochemical examinations, and serum tumor marker assays.

Assay of drug concentrations

The concentration of FT was measured by high-pressure liquid chromatography, and that of 5-FU was measured by gas-mass chromatography according to the method described by Marunaka et al. [25].

Statistical evaluation

The response rate of the primary lesion, the histological effects, and the survival rate after surgery were evaluated to judge the effects of the therapies. χ^2 and Mann-Whittney *U*-tests were used to compare patient backgrounds among the three dosage groups. Overall survival was calculated by the Kaplan-Meier method. A P value of less than 0.05 was considered to be significant. Statistical analysis was carried out using SAS computer software SAS Institute Inc., Cary, NC, USA.

Results

Dose and period of drug administration (Table 2)

UFT was administered at three doses (300, 400, and 600 mg/body per day). The administration period ranged

Table 2. Preoperative dose of UFT

		Early cancer[a] (pT1, $n = 36$)	Advanced cancer[a] (pT2–4, $n = 46$)	Overall ($n = 82$)
Dose (mg/body per day)	300	15	23	38
	400	17	13	30
	600	4	10	14
Period (days)	≤14	11	12	23
	15–28	18	19	47
	≥29	7	5	12
Total dose (g)	≤6.0	14	18	32
	7–12.0	20	23	43
	≥12.1	2	5	7

UFT, Uracil plus futrafur 4:1
[a] According to postoperative pathology

between 7 and 40 days, and the total dose ranged between 2.4 and 21.6 g.

Side effects (Table 3)

Side effects were not serious before surgery: anorexia in 11 patients (13.4%), leukopenia in 3 patients (3.7%), thrombocytopenia in 2 patients (2.4%), and slight liver dysfunction in 2 patients (2.4%). Postoperative complications were seen in 13 patients: 3 patients (3.7%) with suture insufficiency, 1 with perforative peritonitis, and 2 with enteritis due to methicillin-resistant *staphylococcus aureus* (MRSA); all of these patients were cured by conservative therapy or re-operation. Liver dysfunction (serum GOT level > 100 IU/l) was seen in 7 patients (8.5%) and serum GOT levels increased to more than 500 IU/l in 2 patients. It seemed that patients who received UFT for a long period suffered more often from postoperative complications.

Table 3. Side effects (evaluated in 82 patients)

I. Preoperative side effects	
Anorexia	11 (13.4%)
Massive bleeding from gastric cancer	2 (2.4%)
Leukopenia (<300 WBC/mm^3)	3 (3.7%)
Thrombocytoperia (<100 000 platelets/mm^3)	2 (2.4%)
GOT ↑ (>100 IU/l)	2 (2.4%)
II. Postoperative complications	
Suture insufficiency	3 (3.7%)
MRSA enteritis	3 (3.7%)[a]
GOT ↑ (>100 IU/l)	7 (8.5%)[b]

MRSA, Methicillin-resistant *Staphylococcus aureus*
[a] One patient had panperitonitis due to colonic perforation and two patients had enteritis
[b] Two patients had high-level elevation of GOT, of more than 500 IU/l

Objective and histological responses

In 69 of the 82 patients, the sizes of primary tumors before and after UFT administration were compared by endoscopy or upper gastrointestinal series examination, and 2 CRs, 25 PRs, and 42 NCs were seen (27/69, 39.1% response). The involved nodes became smaller in 2 patients, and a single lesion of liver metastasis disappeared in 1 patient. Findings for 4 representative patients who responded to the neoadjuvant UFT treatment are shown in Figs. 1, 2. There was no relationship between the response and the clinical stage (Table 4). Table 5 summarizes the relationship between the response and the dose and administration period. The results also suggest that the dose may not be a very important factor, but longer periods of UFT administration, espe-

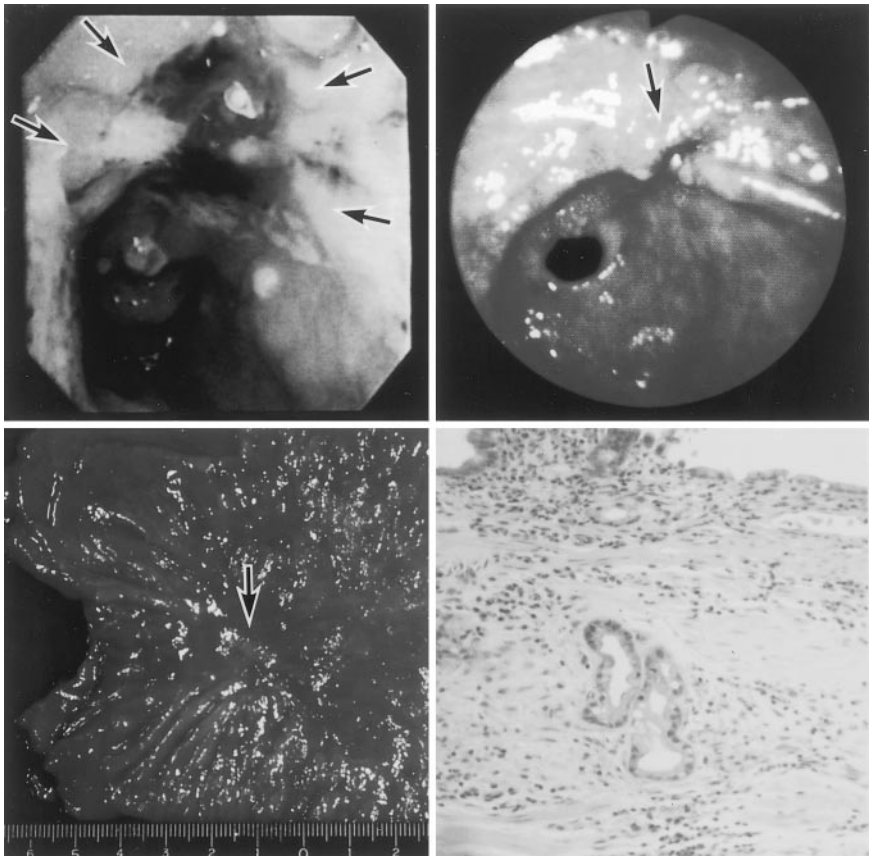

Fig. 1a–d. Representative patient with complete response (CR). The patient, a 70-year-old woman, received uracil + futrafur, 4:1 (UFT) at 300 mg/day for 16 days. **a** Before UFT: IIc-like advanced gastric cancer at lesser curvature of the prepyloric region. **b** After UFT: scar formation of ulcerative lesion; objective response was evaluated as CR. **c** Resected specimen: no macreoscopic lesion was seen. **d** Pathology: minimal lesion of well differentiated adenocarcinoma; the histological response was evaluated as grade 2. The postoperative stage classification was stage 1a: pT1 (m), pN0, M0

Table 4. Macroscopic and histological response after preoperative UFT

Effect	Postoperative stage[a]		
	Stage (1 $n = 40$)	Stage 2–4 ($n = 42$)	Overall ($n = 82$)
Macroscopic response			
CR	2 (5.6%)	0	2 (2.9%)
PR	14 (38.9%)	11 (33.3%)	25 (36.2%)
NC	20 (55.5%)	22 (66.7%)	42 (60.9%)
PD	0	0	0
Unevaluable	4	9	13
Histological effect			
Grade 3	1 (2.5%)	1 (2.4%)	2 (2.5%)
Grade 2	5 (12.5%)	6 (14.3%)	11 (13.4%)
Grade 1b	3 (7.5%)	8 (19.0%)	11 (13.4%)
Grade 1a	13 (32.5%)	14 (33.3%)	27 (32.9%)
Grade 0	18 (45.0%)	13 (31.0%)	31 (37.8%)

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease
[a] pTNM, (UICC 1987)

Table 5. Administered dose and macroscopic response after preoperative UFT (evaluated in 69 of 82 patients)

	CR	PR	NC	PD	Unevaluable
Overall ($n = 82$)	2 (2.9%)	25 (36.2%)	42 (60.9%)	0	13
I. Dose (mg/body)					
300 mg ($n = 38$)	1 (3.0%)	14 (42.4%)	18 (54.5%)	0	5
400 mg ($n = 30$)	0	7 (16.7%)	17 (70.8%)	0	6
600 mg ($n = 14$)	1 (8.3%)	4 (33.3%)	7 (58.3%)	0	2
II. Dose (mg/kg per day)					
≤6.0 ($n = 33$)	0	12 (41.4%)	17 (58.6%)	0	4
6.1–9.0 ($n = 32$)	1 (3.7%)	10 (37.0%)	16 (59.3%)	0	5
≥9.1 ($n = 17$)	1 (7.7%)	3 (23.1%)	9 (69.2%)	0	4
III. Total dose (g/kg)					
<0.1 ($n = 24$)	0	9 (45%)	11 (55%)	0	4
0.1–0.2 ($n = 40$)	1 (3.0%)	11 (33.3%)	21 (36.7%)	0	7
>0.2 ($n = 18$)	1 (6.3%)	5 (31.2%)	10 (62.5%)	0	2
IV. Administration period (days)					
≤14 ($n = 23$)	0	5 (29.4%)	12 (70.6%)	0	6
15–21 ($n = 26$)	1 (4.4%)	7 (30.4%)	15 (65.2%)	0	3
≥2 ($n = 33$)	1 (3.5%)	13 (44.8%)	15 (51.7%)	0	4

cially for more than 3 weeks, may be associated with good objective responses.

The histological effect was evaluated in 82 patients and the following classifications were made: grade 3 (complete disappearance or necrosis of tumor cells), 2; grade 2 (necrotic changes > 2/3 area), 11; grade 1b (>1/3 area), 11; grade 1a (<1/3 area), 27; and grade 0 (no histological changes), 31 (Table 4). There was a correlation between the histological effect and depth of the primary tumor, and the frequences of grade 2–3 responses were significantly higher ($P < 0.05$) in pT4 tumors than in pT1–3 tumors (Table 4). There was no relationship between the histological response and the histology (data not shown). Correlation between the macroscopic and pathological responses is summarized in Table 6, which indicates no correlation between them.

In the present study, 2 patients with CRs were observed. One was a 77 year-old man who had a small Borrman type II advanced gastric cancer at the pyloric ring, and biopsy demonstrated a poorly differentiated adenocarcinoma. After administration of UFT at 300 mg/day for 23 days, endoscopic examination revealed complete disappearance of the ulcerative lesion, and the objective response was evaluated as CR. No ulcerative lesion was found macroscopically in the resected specimen; however, postoperative pathology demonstrated cancer cells infiltrating to the muscularis propria, and the histological response was evaluated as grade 1b. The postoperative stage classification was stage 1b: pT2 (pm), pN0, M0. He died of liver metastasis 46 months after the surgery. The second patient with CR was a 70 year-old women (Fig. 1), who had a large IIc-like advanced gastric cancer, and biopsy

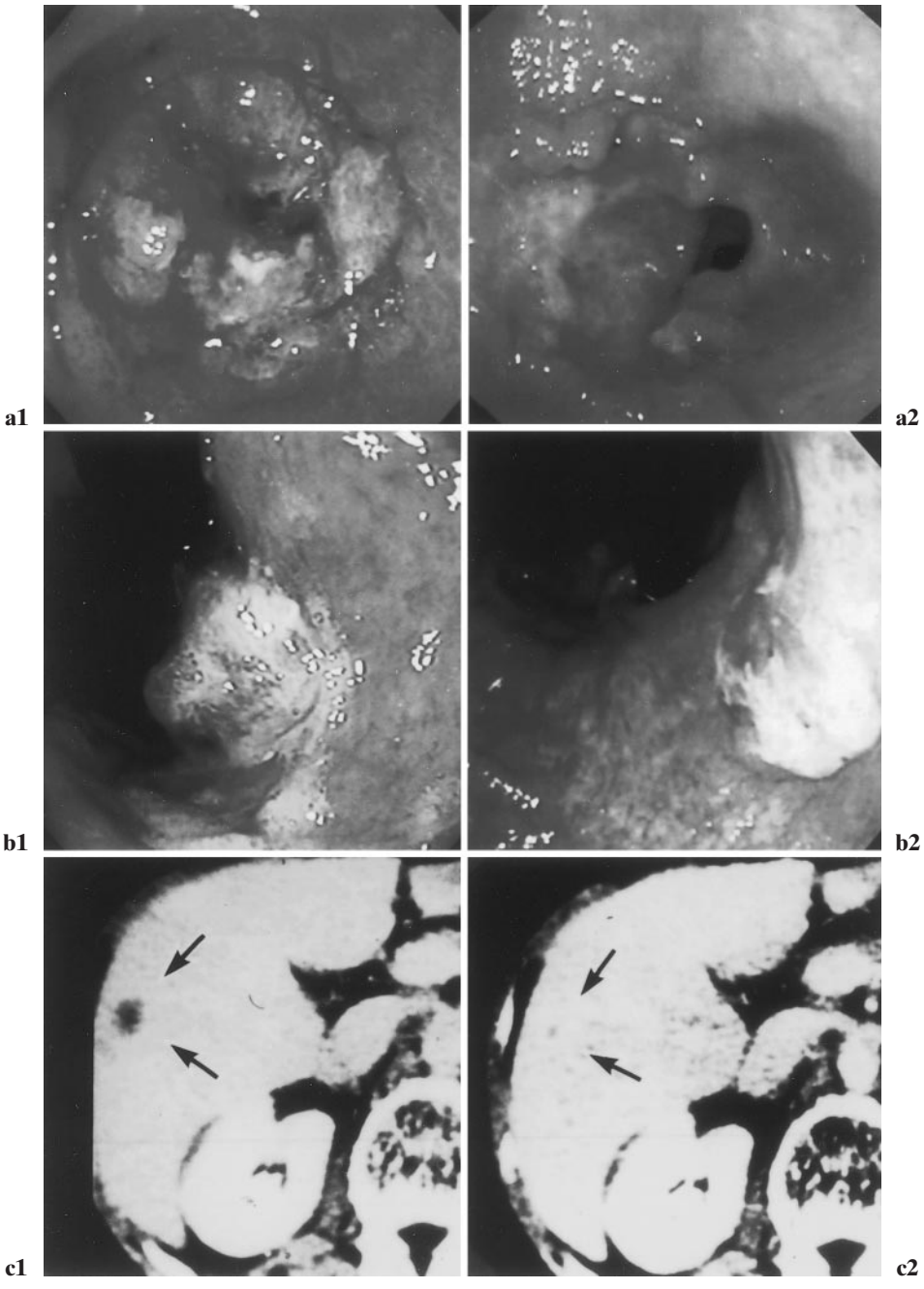

Fig. 2a–c. Representative patients responding to treatment. **a** A 66-year-old woman diagnosed as Bor III (complete pyloric stenosis). **a1** Before and **a2** after UFT 300 mg/day for 12 days. There was a partial response (size reduction) but stenosis was alleviated. **b** A 79-year-old man diagnosed as Bor I. **b1** Before and **b2** after UFT 300 mg/day for 25 days. There was a partial response (size reduction). **c** A 50-year-old man diagnosed with liver metastasis. **c1** Before and **c2** after UFT 600 mg/day for 35 days. There was a partial response in the primary lesion but the liver metastasis disappeared (*arrows*)

Table 6. Correlation between macroscopic and pathological responses

		Grade of pathological response				
Objective response	Total	3	2	1b	1a	0
CR	2	0	1	1	0	0
PR	25	2	4	2	7	10
NC	42	0	4	6	14	18
PD	0	0	0	0	0	0
Unevaluable	13	0	2	2	6	3
Total	82	2	11	11	27	31

demonstrated well-differentiated adenocarcinoma. After administration of UFT at 300 mg/day for 16 days, endoscopic examination demonstrated the scar of the ulcerative lesion, and the objective response was evaluated as CR, and no ulcerative lesion was found macroscopically. At first, the pathologists diagnosed no cancer cells remaining in the resected specimens; however, in a joint meeting of surgeons and pathologists, a minimal lesion was discovered in the submucosal layer, and the histological response was evaluated as grade 2. Her postoperative stage classification was stage 1a: pT1 (m), pN0, M0. Six years have passed since the surgery and

Table 7. Drug concentration in tissues (29 patients)

Dose (/day)	600 mg (n = 6)	400 mg (n = 13)	300 mg (n = 10)
Duration (days)	21.7 ± 10.1	18.8 ± 5.6	20.2 ± 8.5
Primary lesion			
FT μg/g tissue	3.928 ± 3.329 (n = 5)	1.567 ± 1.719 (n = 9)	1.168 ± 0.721 (n = 5)
5-FU μg/g tissue	0.063 ± 0.029 (n = 5)	0.070 ± 0.064 (n = 9)	0.041 ± 0.044 (n = 6)
Normal mucosa			
FT	3.287 ± 3.489 (n = 6)	1.186 ± 1.205 (n = 11)	0.914 ± 0.845 (n = 8)
5-FU	0.039 ± 0.024 (n = 6)	0.031 ± 0.025 (n = 11)	0.011 ± 0.015 (n = 8)
Metastatic node			
FT	1.478 ± 2.688 (n = 3)	3.624 ± 2.700 (n = 4)	0.0 (n = 2)
5-FU	0.069 ± 0.072 (n = 3)	0.041 ± 0.050 (n = 4)	0.0 (n = 2)
Normal node			
FT	1.670 ± 2.893 (n = 3)	1.061 ± 1.314 (n = 12)	0.525 ± 0.734 (n = 8)
5-FU	0.034 ± 0.059 (n = 3)	0.030 ± 0.037 (n = 12)	0.011 ± 0.030 (n = 8)

FT, Futrafur; 5-FU, 5-fluorouracil

Table 8. Comparison of survival rates after surgery in patients who received neoadjuvant UFT and historical controls

	3-year survival rates	
pTNM stage	Control[a]	Neoadjuvant UFT
Stage 1	94.2% (n = 306)	97.1% (n = 40)
Stage 2	78.6% (n = 38)	75.0% (n = 6)
Stage 3	61.3% (n = 78)	86.7% (n = 19)
Stage 4	15.1% (n = 117)	41.6% (n = 17)

[a] Historical controls in our department, 1980–1995

she is now hospitalized for rheumatoid arthritis, with no signs of recurrence.

Drug concentration in tumor tissue (Table 7)

All patients were given UFT at 6:00 p.m. on the day before surgery, and underwent surgery from 9:00 a.m. Blood was drawn at 9:00 a.m. and the tissues were taken between 11:00 a.m. and 3:00 p.m. in the operating room. Table 7 shows the drug concentrations in the cancerous and normal tissues, indicating that larger doses may be associated with a higher concentration of FT in the tissues. However, there were only slight differences in 5-FU concentrations among the three dosage groups.

Survival after surgery

All the patients underwent gastrectomy, and the survival curves after gastrectomy are shown in Fig. 3. During the follow-up period of 12–72 months (median period, 41 months), 16 patients died: 12 due to recurrence of the cancer and 4 of other diseases, including cerebral apoplexy, diabetes mellitus, sepsis caused by pneumonia, and myelodysplasia. Comparative survival rates for patients in this series at our department, and

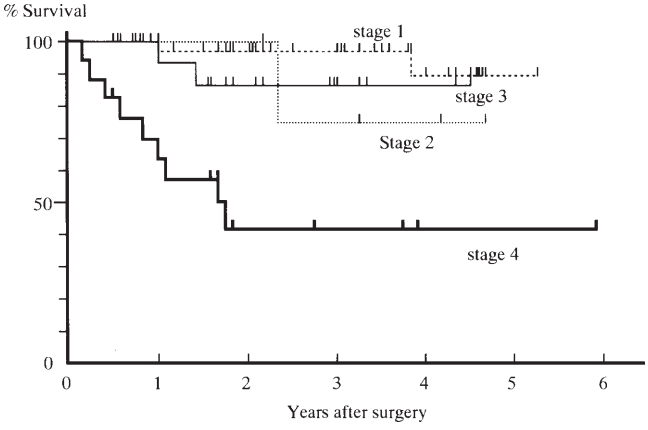

Fig. 3. Postoperative survival curves of patients who received neoadjuvant UFT. During the median follow-up period of 41 months, the 3-year survival rates were 97.1% for patients in stage 1 (n = 40), 75% for those in stage 2 (n = 6), 86.7% for those in stage 3 (n = 19), and 41.6% for those in stage 4 (n = 17)

historical controls at the Japan Cancer Institute Hospital were calculated. The 3-year survival rates were 97.1% for stage 1 (n = 40), 75% for stage 2 (n = 6), 86.7% for stage 3 (n = 19), and 41.6% for stage 4 (n = 17). These survival rates were higher than those of the historical controls in our department (3-year survival rates: 94% for stage 1, 78% for stage 2, 61% for stage 3 and 15% for stage 4) (Table 8).

The correlation between postoperative survival and the objective response is summarized in Fig. 4, indicating no difference in the survival curves between the NC group and the CR or PR groups.

Discussion

Since the reports of Wilke and colleagues [5], neoadjuvant chemotherapy of gastric cancer has

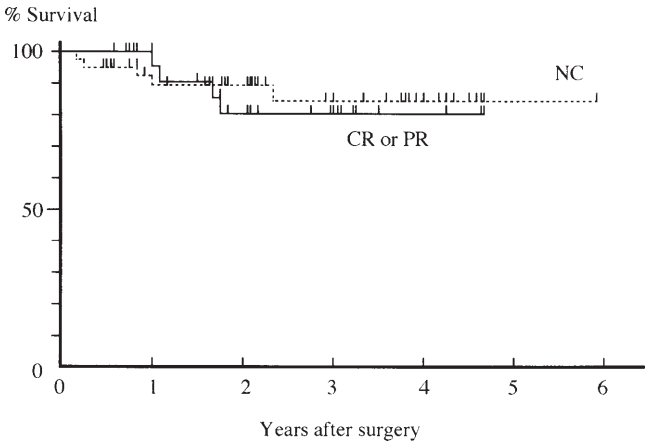

Fig. 4. Objective responses and postoperative survival curves after neoadjuvant UFT. *Dotted lines*, No change (*NC*) (n = 42); *continuous lines*, CR or partial response (*PR*) (n = 27)

attracted the interest of clinical oncologists, and neoadjuvant chemotherapy has been employed for the treatment of various malignancies, such as esophageal, breast, and gastric cancers. The major aim of neoadjuvant chemotherapy is downstaging for resectable cancer and improving the resectability of currently inoperable cancer. In the present study, neoadjuvant chemotherapy with UFT for gastric cancer achieved an objective response of 39%, which is comparable to the responses produced by intensive chemotherapies, and compatible with previous reports on the clinical effects of oral UFT [23]. UFT is widely used for chemotherapy of digestive organ cancers in Japan, and response rates of various cancers to oral UFT are reported to be comparable to those of intensive i.v. chemotherapies, including CDDP, which usually achieve a 20%–40% response rate for gastric cancer. In addition, the side effects of UFT are not so severe [23]. Recently, it has also been reported that a combination regimen with UFT and leucovorin achieved a high response rate in colorectal cancer and was well tolerated [26,27]. These results suggest that UFT may be employed for neoadjuvant chemotherapy instead of intensive i.v. chemotherapy. In the present study, endoscopic examination showed that advanced gastric cancer became similar to early gastric cancer in several patients, and CT examination demonstrated the obvious shrinkage of metastatic nodes and disappearance of liver metastasis in two patients. These responses do not always suggest a preoperative downstaging, but preoperative downsizing of the primary and metastatic lesions was achieved in several patients by UFT.

It is unclear whether neoadjuvant therapy contributes to improved survival after surgery. There have been no reports on this subject, because it is difficult to define the effect of neoadjuvant therapy in the phase II setting. Six years have passed since the start of the present study, but the median follow-up duration is only 41 months. As shown in Table 8, the survival rates of stage 3 and 4 patients were higher than those of the historical controls in our department, although the number of the patients was not sufficient for conclusive results to be drawn. Furthermore, comparisons with historical controls can be severely flawed. In addition, the present study demonstrated that there was no correlation between the objective response and the postoperative survival. Accordingly, if neoadjuvant UFT is truly benefical to improve survival, the macroscopic downsizing of primary tumors may not play an important role. In our previous report, an analysis using Akaike's information criteria demonstrated that the N-factor as well as the T-factor were significant factors affecting the postoperative survival of gastric cancer patients [28]. Accordingly, one possible mechanism for the benefical effect of neoadjuvant chemotherapy on survival may be mediated by its effect on nodal involvment. Since the present study was not a randomized controlled study, such a trial with a larger sample size is necessary to clarify the true effects of neoadjuvant chemotherapy with UFT for gastric cancer.

Oral UFT also has much milder side effects than intensive i.v. chemotherapies. Previous reports showed that 41.4% of patients receiving oral UFT experienced side effects, but that the major side effects were anorexia (24.3%), nausea and vomiting (12.5%), and diarrhea (11.1%); hematological toxicity was noted in only 6.9% of patients [23]. These results suggest an advantage of oral UFT in that patients can receive ambulatory chemotherapy without serious side effects. By contrast, intensive chemotherapy usually requires hospital care, due to its serious side effects, resulting in an impaired quality of life (QOL) and high cost. Accordingly, oral UFT may contribute to improving a patient's QOL and may also reduce treatment costs, making in much more suitable for neoadjuvant chemotherapy of gastric cancer than other intensive i.v. chemotherapies. However, in the present study, three patients became infected with MRSA and seven had moderate liver dysfunction after surgery. While all of these patients recovered, these complications seemed to be associated with the long period of administration (>4 weeks). Accordingly, it is recommended that the dose of oral UFT should be reduced after 2 weeks of administration. Because the frequency of liver dysfunction with UFT therapy is reported to be 0.6% [23], the incidence of postoperative liver dysfunction in the present study seems to be high. The mechanisms responsible for postoperative liver dysfunction are unclear. Fluoropyrimidines, in general, sometimes cause serious liver dysfunction, and various medications after surgery, including drugs used for anesthesia and antibiotics in

the present study, may work synergistically to cause liver dysfunction.

In the present study, UFT was administered at three different doses. Because UFT is an oral agent and one capsule includes 100 mg of FT or one package includes 150 mg of granules, it is difficult to administer a certain does per kg or per m^2, and an obvious dose-dependency has not been seen [23]. The drug concentrations in the tissues may reflect this situation, because the FT concentration in cancer tissue was correlated with the dose administered, but the 5-FU concentration was not (Table 7). The reason for the lack of obvious dose-dependency in chemotherapy with UFT is not clear. After oral administration, UFT may be partly degraded by stomach acid, absorbed by the gut, metabolized into 5-FU by the liver, and then accumulate in tumor tissues. Accordingly, differences among patients in stomach acid activity, gut absorption rates, and metabolizing enzyme activity in the liver may be involved. While no dose-dependent effects were noted in the present study, a higher response rate was seen in patients who received UFT for more than 3 weeks (Table 5). This result seems reasonable because the effect of 5-FU is time-dependent. The results also suggests that 400 mg/body for 3 weeks may be enough to achieve an objective response. In addition, in the present study, postoperative complications, especially MRSA enteritis and suture insufficiency, were seen in patients who received UFT at 400 or 600 mg/body for more than 4 weeks. Accordingly, we recommend neoadjuvant chemotherapy with UFT at 400–600 mg/body for the first 2 weeks and then at 300 mg/body in order to reduce side effects and achieve a high response rate.

In conclusion, the present study indicates that preoperative chemotherapy for gastric cancer with oral UFT may result in clinical downsizing of primary tumors, as well as the prevention of tumor growth before surgery. Furthermore, preoperative chemotherapy with oral UFT is easy and safe, and patients can receive this treatment on an outpatient basis.

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