Patterns of recurrence of gastric cancer following curative gastrectomy depends on adjuvant chemotherapy

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Objective : To compare the pattern of recurrence and the survival rate after two regimens of adjuvant chemotherapy following curative resection of gastric cancer.

Design : Prospective multicentre trial.

Setting : Twenty-one departments of surgery.

Subjects : A total of 163 patients who had undergone histological curative resection.

Interventions : All patients received an intravenous bolus of mitomycin C (20 mg) on the day of operation, and a dose of 10 mg on the first postoperative day. They were then randomized to receive either oral tegafur (600 mg/day) or tegafur-uracil (600 mg/day) for 2 years from 2 weeks after the operation.

Main outcome measures : The pattern of recurrence and the survival rate were assessed.

Results : Tegafur-uracil reduced peritoneal recurrence when compared with tegafur. About 70% of all patients had recurrence within two years. The tegafur-uracil group had a significantly higher 7-year survival rate than the tegafur group ($P=0.04$).

Conclusion : The overall recurrence rate was generally lower in the tegafur-uracil group, although there was no statistical difference. Most of patients had recurrence occurred within 2 years after surgery. This finding indicates that postoperative maintenance therapy for 2 years is necessary to suppress recurrence.

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Gastric cancer shows a higher sensitivity to anticancer agents than most other types of solid cancer. Because of the possibility of recurrence after curative resection of gastric cancer, the killing of residual cancer cells by adjuvant chemotherapy is important to improve the postoperative results¹⁾.

Oral administration of tegafur, a prodrug of 5-FU, to patients with gastric cancer has achieved fairly good results as outpatient adjuvant chemotherapy^{2~8)}.

UFT is a combination of tegafur and uracil at a molar ratio of 1 : 4, and was developed as an antitumor drug by Fujii et al.⁹⁾. Both animal studies and clinical trials have revealed higher levels of 5-fluorouracil (5-FU) in the blood and tumor tissue after UFT administration compared tegafur or 5-FU^{7,10)}. In 1994, we published the results of a 5-year follow-up of 243 gastric cancer patients included in a randomized trial of

tegafur versus UFT³⁾. All patients received an intravenous bolus of mitomycin C on the day of operation and on the first postoperative day. The two regimens had only slight toxicity (nausea, leucopenia, and hepatic impairment) and no adverse effects were observed on the central nervous system. The incidence of toxicity was low, with no significant differences between the groups. In addition, there was no significant difference in the 5-year survival rate (although the patients receiving tegafur-uracil lived longer), except for patients with histological curative resection ($P=0.04$)³⁾. The aim of the present retrospective study was to evaluate differences in the pattern of recurrence between both groups.

Patients and methods

All patients included in this prospective randomized controlled trial had undergone gastric resection during the 27-month period from October 1983 to December 1985 at 21 hospitals in the northern region of Kyushu, Japan. All patients received an intravenous bolus injection of mitomycin C (20 mg) on the day of operation and another 10 mg on the first postoperative day. They were then randomly assigned to one of two groups by the envelope method and received either oral tegafur (600 mg/day) or tegafur-uracil (600 mg/day) for two years from 2 weeks postoperatively for 2 years.

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Table 1 Patients studied

	Curative operation	
	Tegafur	Tagafur-uracil
No. who entered the trial	81	82
No. withdrawn	6	5
No. excluded	4	10
No. studied	71	67

The criteria for patient selection were as follows : macroscopic stage II, III, or IV disease ; age less than 76 years ; no evidence of synchronous or metachronous tumors ; and adequate organ function (white cell count $\geq 4 \times 10^9/L$, platelet count $\geq 750,000/L$, total protein concentration ≥ 60 g/L with an albumin : globulin ratio of 1.0, serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT) ≤ 100 U/L, and no protein urine. Informed consent was obtained from all patients before enrollment.

The total number of subjects at the end of the study was 243,124 in the tegafur group and 119 in the tegafur-uracil group. Thirteen subjects were excluded because they did not have cancer (n=2), they were above the age limit (n=9), they had multiple carcinoma (n=1), or because resection was impossible (n=1). Since the 78 patients in the non-curative resection group showed the same 5-year survival rate²⁾, they were not included in the analysis of results. Therefore, we evaluated 138 patients who had undergone curative resection before adjuvant chemotherapy, excluding 14 patients who did not take the prescribed drug or did not take it as directed (Table 1). It was previously shown that there were no significant differences between the patients with curative resection given tegafur or given tegafur-uracil (Table 2)³⁾.

Recurrence in patients who had undergone curative resection 7 years earlier was classified into the following four patterns based on the results of laboratory tests, laparotomy, and autopsy : localized recurrence, hematogenous recurrence, peritoneal recurrence, and distant lymph node recurrence.

The staging of each patient was performed according to the Japanese guidelines for gastric cancer study¹⁴⁾. The significance of differences between groups was assessed by the chi-square test, the Mann-Whitney U test, and Student's *t*-test. Survival curves were constructed using the Kaplan-Meier method and the significance of differences was assessed by the log-rank test. A P value of less than 0.05 was considered to be significant. Recurrence hazard rates were calculated by Gehan's method¹²⁾.

Table 2 Comparability of the groups

	Curative operation	
	Tegafur (n=71)	Tegafur-uracil (n=67)
Sex :		
Male	39(55)	37(55)
Female	32(45)	30(45)
Age at operation :		
>35	3(4)	1(2)
36-55	25(33)	22(33)
56-75	43(61)	44(65)
Location of tumor :		
Upper	11(15)	17(25)
Middle	29(41)	20(30)
Lower	31(44)	30(45)
Borrmann type :		
0	9(13)	7(11)
1	2(3)	2(3)
2	21(30)	27(40)
3	27(38)	23(34)
4	6(8)	7(10)
5	5(7)	1(2)
Unknown	1(1)	0(0)
Size of tumour(cm) :		
>5	33(46)	24(36)
5-10	29(41)	32(48)
10<	9(13)	11(16)
Histological signs of serosal invasion :		
Absent	42(59)	40(60)
Present	29(41)	27(40)
Histological signs of lymph node metastasis :		
N0	25(35)	22(33)
N1	25(35)	27(40)
N2	18(26)	18(27)
N3	3(4)	0(0)
Macroscopic signs of lymph node metastasis		
N0	5(7)	6(9)
N1	39(55)	32(48)
N2	20(28)	28(41)
N3	6(9)	1(2)
N4	1(1)	0(0)
Histology		
Differentiated	33(47)	36(53)
Undifferentiated	35(49)	31(47)
Unknown	3(4)	0(0)
Histological signs of infiltration at the resection margins :		
Absent	70(99)	67(100)
Present	0(0)	0(0)
Unknown	1(1)	0(0)
Histological stage :		
I	12(17)	10(15)
II	19(27)	21(31)
III	36(51)	34(51)
IV	4(5)	2(3)
Operation		
Total	23(32)	24(36)
Distal partial	46(65)	39(58)
Proximal partial	2(3)	3(5)
Unknown	0(0)	1(1)
Lymph node dissection		
R0	0(0)	0(0)
R1	1(1)	4(6)
R2	59(84)	52(78)
R3	11(15)	11(16)

Figures are number (%) of patients

Table 3 Recurrence patterns and times

Recurrence pattern	Recurrence rate	Recurrence time (year)					
		~ 1	~ 2	~ 3	~ 4	~ 5	5 ~
Tegafur group							
Localized recurrence	8.5% (6/71)	2	3			1	1
Hematogenous recurrence	21.1% (15/71)						
Liver		5	4	1			
Others (lung, bones, etc.)		4	4		2		
Peritoneal recurrence	22.5%* (16/71)	8	4	2	2	1	1
Distal lymph node recurrence	1.4% (1/71)	1					
Tegafur-uracil group							
Localized recurrence	7.5% (5/67)	2	3			1	
Hematogenous recurrence	13.4% (9/67)						
Liver		1	2	2			
Others (lung, bones, etc.)		1	2		1		
Peritoneal recurrence	10.4%* (7/67)	3	2	1			1
Distal lymph node recurrence	1.5% (1/67)			1			
Including overlapping cases							
*P<0.1							

Results

Survival of patients with histological curative resection

The 7-year survival rate for 71 patients in the tegafur group and 67 in the tegafur-uracil group was 45% and 65%, respectively. The tegafur-uracil group showed a significantly better survival rate than the tegafur group ($P=0.04$)(Fig. 1).

Timing and pattern of recurrence (Table 3)

According to the 7-year follow-up results, recurrence occurred in 28 out of 71 patients (39%) in the tegafur group and in 16 out of 67 patients (24%) in the tegafur-uracil group, so the recurrence rate was lower in the latter group ($P=0.07$). Recurrence affected multiple organs in 29%(8/28) of the tegafur group and 31% (5/16) of the tegafur-uracil group. The pattern was localized recurrence in 9%, hematogenous recurrence in 21%, peritoneal recurrence in 23%, and distant lymph node recurrence in 1% of the tegafur group. In the tegafur-uracil group, the mode of recurrence was localized in 8%, hematogenous in 13%, peritoneal in 10%, and lymph node in 2%. Excluding lymph node recurrence, the rates for the other types of recurrences tended to be lower in the tegafur-uracil group, especially in the case of peritoneal recurrence ($P=0.09$). Recurrence generally occurred within 2 years (71% of recurrences in the tegafur group) and 69% of recurrences in the tegafur-uracil group). However, peritoneal recurrence tended to be delayed. One localized recurrence and two peritoneal recurrences occurred after 5 years.

Fig. 1

Survival curves of 138 patients who underwent histological curative operations, 71 of whom received tegafur (closed circles) and 67 of whom received tegafur-uracil (open circle). Vertical marks indicate censored deaths.

Fig. 2 Recurrence hazard rate of all cases

The closed circles indicate patients who underwent curative operation and received tegafur. The open circles indicate patients who underwent curative operation and received tegafur-uracil.

Pattern of recurrence and the recurrence hazard rate

When the hazard rate of recurrence was assessed, peaks were seen in the 1st year (18%, 9%) and the 2nd (14%, 9%) years, followed by a gradual decrease in both the tegafur and tegafur-uracil groups. The hazard rate was generally lower in the tegafur-uracil group (Fig. 2).

The recurrence hazard rates for peritoneal metastasis reached a peak (11%) within 1 year in the tegafur group, while the rate after 1 year was lower but an increased risk was persistent. In the tegafur-uracil group, the recurrence hazard rate (5%) was generally lower than in the tegafur group (Fig. 3). The hematogenous recurrence hazard rate was (8%, 2%) in the 1st year and (7%, 4%) in the 2nd year, followed by a gradual decrease in both groups (Fig. 4).

Fig. 3 Peritoneal recurrence hazard rate
The closed circles indicate patients who underwent curative operation and received tegafur. The open circles indicate patients who underwent curative operation and received tegafur-uracil.

Fig. 4 Recurrence hazard rate (hematogenous relapses)
The closed circles indicate patients who underwent curative operation and received tegafur. The open circles indicate patients who underwent curative operation and received tegafur-uracil.

Discussion

In the management of solid tumors, surgical treatment can remove the primary tumour and any localized disease. However, many patients present with disease which has already extended beyond the primary site and thus cannot be eradicated by surgery. It was suggested in the 1970s that adjuvant treatment of minimal residual disease would provide the best chance of improving the outcome. In western countries, positive results of adjuvant chemotherapy after gastric cancer resection have been regarded skeptically¹³. This may explain why most of the studies published after 1985 have been performed in Japan and have generally employed MMC and/or 5-fluorouracil derivatives²⁻⁶.

The 7-year survival rate after curative resection of gastric cancer was determined in this study, and it was found that a rather large number of patients suffered recurrence. Recurrence of gastric carcinoma generally develops within a

short time after surgery¹⁴, but there have also been reports of late relapse and such cases have increased recently¹⁵.

The most common classifications of the pattern of recurrence depend on the mode of tumor progression and include localized recurrence, lymphatic recurrence, peritoneal recurrence beyond the range of surgical resection, and hematogenous metastasis^{15, 16}. However, as pointed out by Iwanaga et al.¹⁵, localized and lymph node recurrence appear to progress to peritoneal and hematogenous recurrence, making it important to study the initial form of tumor relapse. However, since recurrence at multiple sites is common by the time of discovery, all organs affected by recurrence were investigated in this study.

We classified recurrence into four patterns (localized, peritoneal, hematogenous, and lymph node recurrence) based on the site and extent of tumor recurrence. There were few cases of localized recurrences or lymph node metastasis, while peritoneal and hematogenous recurrence were common in both groups, probably because the patients had undergone curative resection.

In patients with gastric cancer who have undergone curative resection, adjuvant therapy with mitomycin C is reported to be more useful than surgery alone, the most frequent site of relapse is the peritoneal cavity and there is a marked decrease of liver metastases in treated patients^{5, 17}. It has also been reported that long-term oral tegafur combined with a short course of high-dose mitomycin C was more useful than short-term mitomycin C alone^{4, 6}.

In 1975, the Adjuvant Chemotherapy Study Group for Gastric Cancer Surgery was organized on a wide nation scale in Japan. The first study employed mitomycin C and tegafur administered for 3 months⁶. In the second study, administration of tegafur was continued for one year⁴.

The survival rate was improved by bolus administration mitomycin C (20 mg on the day of the operation and 10 mg on the following day) and continuous oral tegafur (600~800 mg/day) for 3 months from the 2nd week after the operation, and the survival rate was significantly improved compared to patients receiving mitomycin C alone⁶. In a study on recurrence hazard rates, high-dose mitomycin C and maintenance therapy with tegafur were shown to be useful in preventing recurrence by peritoneal metastasis in stage III¹⁴.

In the second study, short-term administration of mitomycin C followed by tegafur for one year achieved similar results to those found in the first study. Peritoneal and hematogenous metastasis were inhibited by long-term tegafur, and both the disease-free interval and the survival time were prolonged⁴. However, when the recurrence hazard rates were determined, peaks were seen within 0.5~1.5 years for all types of recurrence, and the highest hazard rate was observed for peritoneal metastasis¹⁴.

UFT is an analogue of 5-FU that has been used clinically⁷. Ikenaka et al.¹⁸ reported that uracil suppresses the

degradation of 5-FU but not the phosphorylation of 5-FU *in vitro*, while UFT has a higher therapeutic ratio and a broader spectrum of antitumor activity than 5-FU in experimental tumors⁹⁾. When UFT was given to rodents⁹⁾ or patients^{4, 7)}, higher levels of 5-FU were found in the blood and tumor tissue compared with administration of tegafur or 5-FU. In a phase II study, the response rate of various tumors was 15.6% for tegafur and 27.6% for tegafur-uracil, while the response rates of gastric cancer were 23% and 30%, respectively¹⁷⁾. Accordingly, we compared UFT with tegafur as maintenance therapy for patients with stage II, III, or IV gastric cancer³⁾. Short-term mitomycin C therapy was followed by 2 years of tegafur or tegafur-uracil, we found that the 7-year survival rate showed the same trends as the 5-year survival rate³⁾.

Although there was no statistical difference, the overall recurrence rate was 39% in the tegafur group and 24% in the tegafur-uracil group. Peritoneal and hematogenous recurrence rates were lower in the tegafur-uracil group, but there was no significant difference in the pattern of recurrence. However, some small differences between the groups may exist. To detect a 10% difference at the $P < 0.05$ levels would require 500 patients in each arm of a trial¹⁹⁾, but the clinical relevance of such a difference would be questionable. Thus, these therapies may show significant difference if a larger number of eligible patients are studied.

About 70% of all recurrences occurred within 2 years in both groups. The risk was highest within 2 years for all modes of relapse, and thereafter fell sharply¹⁴⁻¹⁶⁾. This finding indicates that postoperative maintenance therapy for 2 years is necessary to suppress recurrence.

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