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A Cooperative Randomized Study on Tegafur plus Mitomycin C versus Combined Tegafur and Uracil plus Mitomycin C in the Treatment of Advanced Gastric Cancer

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A randomized controlled trial involving 13 institutions in Japan was conducted in order to compare the efficacy of tegafur plus mitomycin C (MMC) (Regimen A) and UFT (a combination of uracil and tegafur at a molar ratio of 4 to 1) plus MMC (Regimen B) for patients with advanced gastric cancer, who had not received any prior cancer chemotherapy. Regimen A (tegafur + MMC) consisted of 5 mg of MMC/m^2/week given intravenously, and 500 mg of tegafur/m^2/day given orally. Regimen B consisted of the same schedule of MMC and 375 mg of UFT/m^2/day given orally. One hundred and eighty-six patients with primary gastric cancer were entered; 183 were eligible and 3 were ineligible for the study. A total of 169 were evaluable for efficacy of the treatment, including 90 patients with Regimen A and 79 with Regimen B. A response rate of 7.8% (7/90 cases) for Regimen A and one of 25.3% (20/79 cases) for Regimen B were obtained, indicating a significantly higher response rate for Regimen B according to the Criteria for Evaluating Efficacy of Chemotherapy/Radiation Therapy in the Treatment of Gastric Cancer ($P=0.004$). Regarding side effects, no marked differences in either severity or incidence were observed between the two groups. The group assigned to Regimen B showed a significant survival advantage after adjustment for major prognostic factors using a proportional hazards model ($P=0.0398$). Moreover, a close correlation of antitumor effect and survival duration was found when the above criteria were used.

Key words: Randomized study — Tegafur — Tegafur and uracil — MMC — Gastric cancer

Despite the improved methodology for diagnosis of gastric cancer at an early stage, many patients with inoperable or recurrent gastric cancer receive chemotherapy in Japan. A variety of combination chemotherapies including fluoropyrimidines such as tegafur and UFT (a combination of uracil and tegafur at the molar ratio of 4 to 1)[1, 2] have been employed for the treatment of patients with advanced gastric cancer.[3–6] When the primary tumor was successfully treated with anticancer drugs and the response was confirmed radiologically and endoscopically, the survival increased.[4, 5, 7] However, unfortunately the results of various clinical trials covering a large number of patients have not met the international criteria for chemotherapy of gastric cancer. A multi-institutional controlled study was developed by the Gastric Cancer Study Subgroup of the Cooperative Study Group of Multidisciplinary Therapy for Solid Tumors supported by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan. Tegafur plus mitomycin C (MMC) has been commonly used in the management of advanced gastric cancer. UFT, developed by Fujii *et al.*,[1, 2] shows a selective antineoplastic effect, because biochemical modulation by uracil enhances 5-FU concentration more specifically in tumor tissues than in normal tissues.[8] The efficacy of UFT on gastric cancer, especially in combination with MMC, was confirmed by Suga *et al.*[5] In the present study, patients with unresectable gastric cancer were

randomly assigned to either of the two regimens: tegafur plus MMC (Regimen A) and UFT plus MMC (Regimen B).

MATERIALS AND METHODS

Patient population and eligibility The patients entered into this study had adenocarcinoma which was histologically proven by biopsy and/or autopsy, and had received no prior chemotherapy. All patients had an unresectable primary focus evaluated by X-ray examination and/or endoscopy, and metastatic lesions evaluated by X-ray, CT scan, US scan or palpation. They were not more than 80 years old and had a Karnofsky's performance status (PS) of 20–100%: adequate bone marrow, renal and hepatic function: a minimum life expectancy of at least 2 months and ability to be treated orally.

Stratification and treatment methods Patients were stratified by tumor spreading type into the following three groups before entry into the study: abdominal localized type, liver metastatic or ascitic type and distant metastatic type. They were randomly assigned by a central office to therapy regimens according to the tumor spreading type. In Regimen A, patients were treated with 5 mg/m^2 of MMC intravenously on a weekly basis and 500 mg/m^2/day of tegafur (enteric granules) orally. In Regimen B, patients were treated with 5 mg/m^2 of MMC intravenously on a weekly basis and 375 mg/m^2/day of UFT orally. Dose modifications were made based on blood analysis: for WBC between 3,000 and 3,500/mm^3, platelets 80,000 to 10,000/mm^3, bilirubin 1.2–3$\times$N, GOT or GPT 2–3$\times$N and urea N 1.2–1.5$\times$N, the dose of MMC and/or UFT was decreased by 25% of the initial dose; for WBC between 2,500 and 3,000/mm^3 and platelets 60,000 to 80,000/mm^3, the dose of MMC and/or UFT was decreased by 50% of the initial dose. For WBC less than 2,500/mm^3, platelets less than 60,000/mm^3, bilirubin more than 3$\times$N, GOT or GPT more than 3$\times$N and urea N more than 1.5$\times$N, MMC and/or UFT were discontinued. No dose modification was made for tegafur.

Response criteria The following are the Criteria for Evaluating Efficacy of Chemotherapy/Radiation Therapy in the Treatment of Gastric Cancer established by the Japanese Research Society for Gastric Cancer, which are described in the 11th Revised Version of the General Rules for the Gastric Cancer Study.[9] These criteria classify the primary foci of inoperable gastric cancer into three subtypes by X-ray or endoscopic findings: measurable lesion (a-lesion), not measurable but evaluable lesion (b-lesion) and diffusely infiltrated lesion (c-lesion). Complete response (CR) is defined as disappearance of tumor on X-ray or endoscopy for a minimum of 4 weeks. According to the three subtypes, CR of each lesion is noted as aCR, bCR and cCR respectively. aPR (partial response) requires a minimum of 50% reduction in the sum of the products of the greatest perpendicular diameters of measurable lesions. bPR requires a marked regression and flattening of elevated or ulcerated lesions (an estimated decrease of more than 50%) on X-ray or endoscopy for a minimum of 4 weeks. cPR requires a minimum of 100% enlargement of the affected area in X-ray films for a minimum of 4 weeks. aNC (no change) and bNC are defined as no change in comparison with pretreatment findings or no changes suitable to be categorized as PR for a minimum of 4 weeks. cNC is defined as less than 100% enlargement of the affected area in X-ray films for a minimum of 4 weeks. aPD (progressive disease) and bPD are defined as a 25% or greater increase of a-lesion and an estimated 25% or greater increase of b-lesion on X-ray or endoscopy, respectively. cPD is defined as tumor progression detected by X-ray examination. Response criteria for metastatic lesion are almost the same as the WHO criteria.

RESULTS

Case analysis and background factors All the registered patients (January 1985–October 1988) had been confirmed by central office and 186 patients were considered to meet the eligibility criteria for the study. Among them three were excluded from the study as ineligible and 183 (98.4%) were evaluated as eligible. The three ineligible patients suffered from double cancer (stomach and colon), operable cancer and gastric cancer at an early stage. Fourteen of the eligible cases were judged to be incomplete because of withdrawal (6 cases), drop-out (7 cases) or incomplete observation (1 case). Thus there were 169 evaluable patients (90.9%) consisting of 90 for Regimen A and 79 for Regimen B.

Among the eligible patients, no differences in background factors were seen according to treatment regimen because of the careful stratification before entry into the study. There was no difference in macroscopic or histologic classifications or lesion subtype (a-, b- and c-lesions) according to the Response Criteria for Evaluating Efficacy of Chemotherapy/Radiation Therapy in the Treatment of Gastric Cancer (Table I).

For complete cases, the total administered doses were examined by treatment regimen. The total dose of UFT (Regimen B) appears to be less than that of tegafur (Regimen A); however, this is due to a difference in the daily dose. When evaluated in terms of duration of administration, the doses of UFT and tegafur administered were almost the same. No difference was reported in the total dose of MMC between the two regimens (Table II).

Table I. Background Factors for Eligible Patients

	No. of patients	Regimen A 97	Regimen B 86	Total 183	χ^2-test
Sex	Male	63	62	125	$P=0.380$
	Female	34	24	58	
Age	–39	4	3	7	$P=0.825$
	40–49	9	8	17	
	50–59	18	19	37	
	60–69	37	26	63	
	70–	29	30	59	
PS	20	0	1	1	$P=0.529$
	40	4	5	9	
	50	6	6	12	
	60	10	10	20	
	70	22	13	35	
	80	15	22	37	
	90	31	21	52	
	100	9	8	17	
Tumor spreading type					
abdominal localized type		33	28	61	$P=0.968$
liver metastatic or ascitic type		46	41	87	
distant metastatic type		18	17	35	
Macroscopic type					
Borrmann	1	7	4	11	$P=0.646$
〃	2	10	15	25	
〃	3	41	36	77	
〃	4	33	27	60	
unclassified		6	4	10	
Histology[a)]					
Pap		4	2	6	$P=0.648$
Tub		47	39	86	
Por		33	28	61	
Sig		13	16	29	
Others		0	1	1	
Gastric lesion subtype					
a-lesion		31	28	59	$P=0.973$
b-lesion		34	31	65	
c-lesion		32	27	59	

a) The following abbreviations are taken from "The General Rules for the Gastric Cancer Study"[21]: Pap (papillary adenocarcinoma), Tub (tubular adenocarcinoma), Por (poorly differentiated adenocarcinoma), Sig (signet-ring cell carcinoma).

Antitumor effect The overall response rate for Regimen A was 7.8% and that for Regimen B was 25.3% in complete cases, indicating that Regimen B (UFT plus MMC) was superior to Regimen A with a significant difference (χ^2 test $P=0.004$). In particular, in the case of abdominal localized type and liver metastatic or ascitic type (both types had a similar outcome), Regimen B showed a significant advantage and one case of complete response was obtained (Table III). Regimen B was superior to Regimen A for a-lesions ($P=0.036$).

When efficacy was assessed by target lesion, the effect on gastric lesions was slightly lower than the overall effect including effect on metastatic lesions; however, the superiority of the response rate for Regimen B to that for Regimen A was demonstrated in the gastric lesions (7.1% for Regimen A versus 22.1% for Regimen B). In

Table II. Dosage Status (Complete Cases)

	Regimen A (Tegafur)	Regimen B (UFT)
Tegafur/UFT		
Total dose (g)		
<20.0	5	24
20.0–29.9	17	14
30.0–39.9	16	15
40.0–49.9	12	10
50.0–59.9	8	4
60.0–69.9	7	5
70.0–79.9	5	4
≧80.0	20	3
Administered duration (weeks)		
<4	4	4
4–7	33	27
8–11	24	22
12–15	12	9
16–19	5	10
≧20	12	7
MMC		
Total dose (mg)		
<20.0	1	1
20.0–29.9	9	8
30.0–39.9	15	16
40.0–49.9	19	18
50.0–59.9	17	13
60.0–69.9	20	12
70.0–79.9	5	5
≧80.0	4	6

the case of liver metastasis, Regimen B was also more effective than Regimen A. No difference was seen in effect on lymph node metastasis and ascitic tumor; however, the number of cases was small (Table IV).

Prolongation of survival When the survival rate for eligible cases including incomplete cases was studied, the 50% survival time was 180 days for both Regimens A and B (Fig. 1). This was partially attributable to inclusion of poor performance status (20–40%) cases. When we used a longer duration basis, i.e., 1 to 1.5 years, the 1-year survival rate for Regimen A was 13.9%, and that for Regimen B was 22.4%, while the 1.5-year survival rate for Regimen A was 5.8%, and that for Regimen B was 14.8% (Logrank test: $P = 0.306$, generalized Wilcoxon test: $P=0.4022$). Based on the proportional hazards model,[10] eight background factors of the patients, including regimen, were analyzed. The differences in regimen ($P=0.0398$), tumor spreading type, lesion subtype and performance status ($P<0.0001$) were found to significantly affect survival; these results corresponded to our clinical experience.[7, 11]

Some factors such as abdominal localized type ($P<0.0001$), a-lesion ($P=0.0050$) and performance status greatly influenced survival. Furthermore, the difference in regimen was found to be an important factor in determining prognosis, and when adjustment was made for the above-mentioned factors, Regimen B therapy was believed to be more favorable to survival than Regimen A (Table V).

Table III. Antitumor Effect

	Regimen	CR	PR	NC	PD	Response rate (%) (CR+PR)	U-test χ^2-test
Tumor spreading type							
abdominal	A		1	26	4	1/31 (3.2)	$P=0.050$
localized type	B	1	5	20	2	6/28 (21.4)	$P=0.079$
liver metastatic	A		3	22	17	3/42 (7.1)	$P=0.025$
or ascitic type	B		10	18	9	10/37 (27.0)	$P=0.038$
distant	A		3	5	9	3/17 (17.6)	$P=0.696$
metastatic type	B		4	3	7	4/14 (28.6)	$P=0.770$
Gastric lesion							
a-lesion	A		3	16	7	3/26 (11.5)	$P=0.047$
	B	1	10	11	5	11/27 (40.7)	$P=0.036$
b-lesion	A		3	14	16	3/33 (9.1)	$P=0.017$
	B		7	15	6	7/28 (25.0)	$P=0.185$
c-lesion	A		1	23	7	1/31 (3.2)	$P=0.850$
	B		2	15	7	2/24 (8.3)	$P=0.819$
Overall							
Total	A		7	53	30	7/90 (7.8)	$P=0.007$
	B	1	19	41	18	20/79 (25.3)	$P=0.004$

Table IV. Efficacy by Tumor Site

		CR	PR	NC	PD	Response rate (%)	U-test χ^2-test
Stomach	Regimen A		6	66	12	6/84 (7.1)	P=0.047
	Regimen B	3	14	50	10	17/77 (22.1)	P=0.013
Liver	Regimen A	1		18	13	1/32 (3.1)	P=0.0004
	Regimen B		10	19	3	10/32 (31.3)	P=0.008
Lymph node	Regimen A		3	9	8	3/20 (15.0)	P=0.178
	Regimen B	2	2	6	3	4/13 (30.8)	P=0.518
		Effective	No change	Ineffective		Response rate (%)	U-test χ^2-test
Ascites	Regimen A	4	6	7		4/17 (23.5)	P=0.544
	Regimen B	2	5	2		2/9 (22.2)	P=0.679

Table V. Analysis of Survival Effect Based on Major Background Factors with the Proportional Hazards Model

Variable	Beta	Standard error	χ^2	P	R	Z:PH
Regimen(A: 0, B: 1)	−0.34871717	0.16960301	4.23	0.0398	−0.041	−0.83
PS	−0.02460966	0.00514746	22.86	0.0000	−0.126	1.01
Localized type	−1.00637083	0.18760806	28.77	0.0000	−0.143	1.91
a-Lesion	−0.51472768	0.18321442	7.89	0.0050	−0.067	0.24

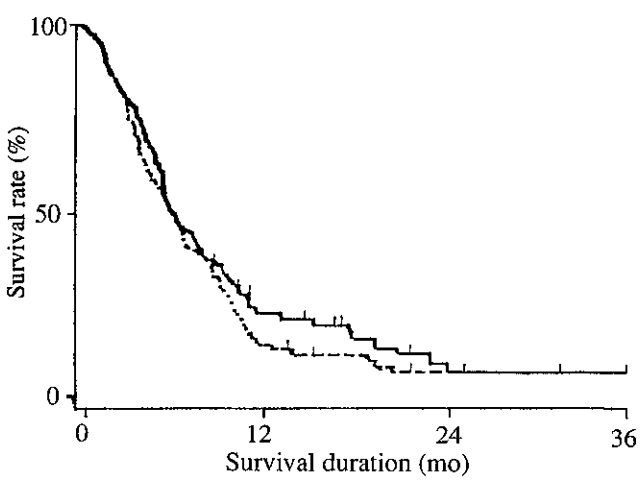

Fig. 1. Survival curves of patients given Regimen A (----) and Regimen B (——). Median survival period: 180 days in both regimens.

The survival rate for the 169 complete cases of both regimens was analyzed by tumor spreading type, lesion subtype and overall response rate. Higher survival rates were observed for the patients with abdominal localized tumor spreading type (Fig. 2a), and those with a-lesions (Fig. 2b). In an overall evaluation, the effectively treated patients had a higher survival rate (Fig. 2c), suggesting that the antitumor effect was closely related to the survival.

DISCUSSION

In Japan there is a high incidence of inoperative primary gastric cancer among elderly patients and they are apt to receive chemotherapy. Regimen A, tegafur (500 mg/m^2/day) plus MMC (5 mg/m^2/day), has been most widely used in the treatment of advanced gastric cancer. In 1984, Suga *et al.*[5] reported that the objective response rate (including disappearance of ascites) for UFT (375/mg/m^2/day) plus MMC (4.0–5.3 mg/m^2/week) was 15/22 (68.2%) for Borrmann type 4 gastric cancer. Therefore, two regimens were compared in this study: Regimen A versus Regimen B. Suga, one of the participants in this study, stated that an adequate dose of UFT was 375 mg/m^2/day, which caused almost the same hematological side effects as 500 mg/m^2/day of tegafur, at the time when the protocol was designed. We conducted a randomized controlled trial involving 13 institutions which had much experience in the treatment of gastric cancer.

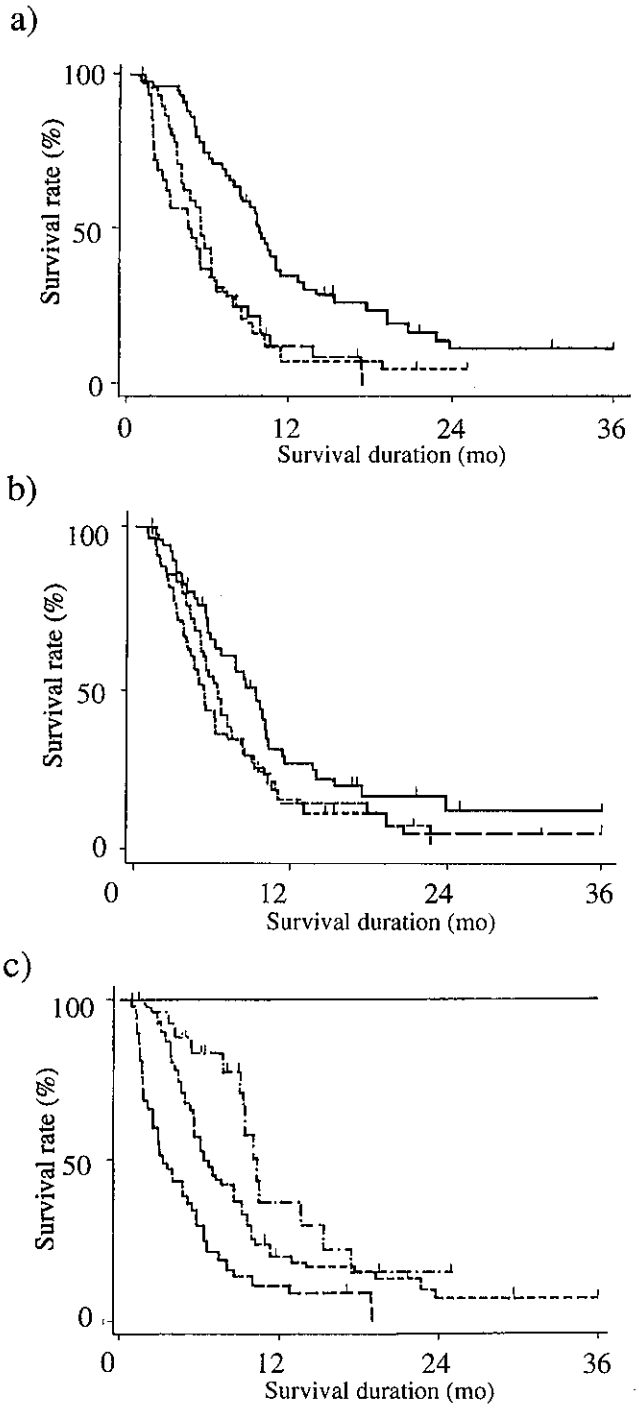

Fig. 2. a. Survival curves for patients by classification of tumor spreading type; abdominal localized type (——), liver metastatic and/or ascitic type (----), and distant metastatic type (— —). Median survival period: 295 days, 165 days and 136 days, respectively. Abdominal localized type vs. liver metastatic and/or ascitic type $P=0.0001$, abdominal localized type vs. distant metastatic type $P=0.0001$ (generalized Wilcoxon test). b. Survival curves for patients by classification of gastric primary focus. a-Lesion (——), b-lesion (----) and c-lesion (— —). Median survival period: 282 days, 161 days and 189 days, respectively. a-Lesion vs. b-lesion $P=0.0073$ (generalized Wilcoxon test). c. Survival curves for patients by overall response rate; CR (——), PR (—·—), NC (----) and PD (— —). Median survival period: PR, 312 days; NC, 198 days; PD, 97 days; PR vs. NC $P=0.01$, NC vs. PD $P=0.0001$ (generalized Wilcoxon test).

In this study Regimen B showed a significantly superior response rate to tegafur plus MMC, although there were no significant differences in treatment duration, dose of MMC administered, and bone marrow, liver and renal toxicity. The results indicate that UFT plays a role of biochemical modulation, inducing a higher concentration of 5-FU in the tumor than does tegafur. Regimen B also showed a marked effect not only on the primary gastric tumor, but also on metastases in the liver, lymph node and ascites. A response rate of 25.3% is not particularly high when compared with those reported in the American and European literatures.[12–18] However, we would like to point out the following characteristics of our study subjects in order to explain this low response rate: 1) all patients had inoperable primary gastric cancer; 2) 34.2% of the patients were more than 70 years old; 3) 16% of patients had a 20–50% Karnofsky's PS; and furthermore 4) the patients were strictly evaluated by roentgenography and endoscopy for primary gastric lesion, and by abdominal US scan or CT scan for metastatic lesions according to the Criteria for Evaluating of Chemotherapy/Radiation Therapy in the Treatment of Gastric Cancer established by the Japanese Research Society for Gastric Cancer.[9] Therefore, a direct comparison of the results with those of other studies that did not use the same evaluation methods might lead to incorrect interpretation of the data.

In 1980, Kurihara and Izumi[19] reported that out of 109 patients undergoing chemotherapy for advanced gastric cancer, only seven (6.4%) achieved a tumor reduction of over 50% based on X-ray findings, while eight of 68 patients who had palpable intra-abdominal masses (62.4% of the 109 patients) were evaluated to have a PR by palpation (an 11.8% response rate). This may have reflected the fact that only a very few patients with inoperable gastric cancer have primary foci that are measurable by roentgenography or endoscopy, and that it is extremely difficult to measure the size of the primary foci accurately in the majority of such patients. These circumstances led to the establishment of The Response

Criteria for Evaluation Efficacy of Chemotherapy/Radiation Therapy in the Treatment of Gastric Cancer. It was possible to evaluate the actual efficacy of chemotherapy on advanced gastric cancer when type a-, b- and c-lesions were judged separately. The survival curves of b- and c-lesions were not different, although the response rate for the two lesions is significantly different. The PR criterion for c-lesions needs to be re-examined.

All the patients who had an inoperable primary gastric tumor and received no prior treatment were stratified by tumor spreading type into three groups on the basis of the following data: Kimura *et al.*[20] reported in 1967 that the median survival of patients with gastric cancer treated with chemotherapy was 7.5 months for the abdominal localized type, 3.7 months for the liver metastatic type, 3.5 months for the ascitic type and 3.1 months for the distant metastatic type. In 1981, the median survival of patients with the same types treated with chemotherapy was reported by Kurihara[11] to be 10 months for the abdominal localized type, 4.5 months for the liver metastatic type, 4.0 months for the ascitic type and 3.5 months for the distant metastatic type. In this study the longest survival occurred in the patients with the abdominal localized type, but similar survival duration was achieved in the other two types; patients with liver metastatic and/or ascitic type and distant metastatic type. Consequently, it may be sufficient to stratify patients into two groups, namely abdominal localized type and others, in the next study.

There was no significant difference in the 50% survival time between the two regimens. This was calculated 6 months from the beginning of the treatment and also indicated similar survival to other studies.[3, 6, 13] However, Regimen B produced the following survival rates: a 22.4% 1-year survival rate and a 14.8% 1.5-year survival rate. On the other hand, Regimen A showed a 13.9% 1-year survival rate and a 5.8% 1.5-year survival rate.

Therefore, in order to further clarify the efficacy of Regimen B at the next step, it may be worth comparing it with other regimens, for instance two or three newly developed drug combination therapies including CDDP with a high response rate[14–16] due to a good performance status of 0–2 on the ECOG scale.

The survival durations for all patients according to efficacy were 312 days for patients with PR, 189 days for NC and 108 days for PD, showing a significant difference in antitumor effect. Although WHO criteria have not been able to reveal the correlation between survival duration and PR and NC status, our study suggests that when the above-described new Japanese criteria are adopted, in other words, on the basis of more definite evaluation of the outcome of chemotherapy than in the WHO criteria, there is a clear correlation between antitumor effect and survival duration. Additional studies to verify this are imperative.

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