Table 4. RRs and 95% CIs of gastric cancer by anatomical subsite in relation to green tea consumption among women

	Green tea consumption (cups per day)				
	<1	1–2	3–4	5+	*p* for trend
All site					
RR[a] (95% CI), n = 225	1.0	0.93 (0.61–1.41)	1.10 (0.75–1.60)	0.70 (0.47–1.05)	0.15
RR[b] (95% CI), n = 203	1.0	0.85 (0.53–1.38)	1.04 (0.68–1.58)	0.67 (0.43–1.04)	0.08
Upper-third including cardia					
RR[a] (95% CI), n = 21	1.0	2.28 (0.56–9.33)	0.70 (0.13–3.62)	1.74 (0.44–6.86)	0.73
RR[b] (95% CI), n = 19	1.0		0.89 (0.34–2.33)		0.81
Distal					
RR[a] (95% CI), n = 169	1.0	0.92 (0.58–1.47)	1.05 (0.69–1.60)	0.53 (0.33–0.85)	0.01
RR[b] (95% CI), n = 154	1.0	0.88 (0.52–1.49)	1.00 (0.63–1.59)	0.51 (0.30–0.86)	0.01

[a] Calculated from a proportional hazards regression analyzing the two cohorts together. Adjusted for age, area, and cigarette smoking.
[b] Calculated from weighted average of the results from separate proportional hazards regressions fitted to the individual cohorts. Further adjusted for consumption of fruit, green or yellow vegetables, fishgut, miso soup, rice, black tea, and coffee.

Discussion

In the present study, a reduced risk of gastric cancer in relation to green tea consumption was observed among women. This relationship was more notable when the tumor was localized to the distal stomach. Several explanations may be possible regarding the null association for men: the highest category included more subjects with higher consumption of green tea in women compared to men; the protective effect may be truly confined to women; the observed association in women was a mere chance finding; and the assessment of tea consumption may have been less accurate in men than in women. We have determined that the validity of green tea consumption assessed with a dietary record for 28 days is slightly lower in men compared to women, both in Cohort I and Cohort II; Spearman correlation coefficient 0.57 for men and 0.63 for women in Cohort I [22] and 0.37 for men and 0.43 for women in Cohort II (unpublished data). Another explanation is that it may be due in part to residual confounding effects, especially for cigarette smoking, in men. In our previous analysis [23], we observed a nearly twofold statistically significant increased risk of gastric cancer in relation to cigarette smoking in men. This point may also be applied to the previous cohort studies, in which potential confounding factors such as consumption of vegetables and fruits as well as cigarette smoking may not have been sufficiently controlled for. Even in these prospective studies, although not statistically significant, lower risk estimates of gastric cancer were observed among women compared to men. Tsubono *et al.* showed that adjusted RRs of gastric cancer risk for green tea consumption of 1–2, 3–4, and 5 or more cups per day were 0.8 (95% CI 0.5–1.5), 0.7 (0.4–1.3), and 0.8 (0.5–1.3), respectively, as compared with consumption of one cup per day or less in women while the corresponding values were 1.3 (0.8–1.9), 1.2 (0.8–1.8), and 1.5 (1.0–2.1) in men [6]. Furthermore, another recent study from Japan revealed that adjusted RRs of gastric cancer death for green tea consumption of 5–9, and 10 or more cups per day were 0.8 (95% CI 0.4–1.6) and 0.7 (0.3–2.0), respectively, in women. For men, the corresponding values were 1.1 (0.6–1.9) and 1.0 (0.5–2.0) [8].

Upper-third gastric cancer had no association with green tea consumption. This was observed both in men and women. Few studies have investigated the relationship between green tea consumption and gastric cancer risk considering anatomical subsite, all of which were case-control studies [24, 25]. While Ji *et al.* [25] showed no difference in risk estimates by subsite (cardia versus distal), Yu *et al.* [24] showed a different risk pattern by tumor subsite; the effect estimate for tea drinkers compared to nondrinkers was near null for the cardia site (OR = 0.95, 95% CI = 0.51–1.77) and was more notable for the pyloric site (OR = 0.29, 95% CI = 0.13–0.68) and antrum site (OR = 0.67, 95% CI = 0.41–1.08). The inconsistencies among studies may be due to some extent to different levels of misclassification of cardia cancers, such as the recent introduction of a separate diagnostic code, the lack of consensus for a definition of cardia, and an increased interest in cardia cancer [10, 26]. Yu *et al.* [24] also showed that boiling hot tea had a nonsignificant increased risk of gastric cancer (OR = 1.18, 95% CI = 0.75–1.86). The risk estimates for the cardia, pylori, and antrum sites regarding boiling hot tea were 2.09, 0.56, and 0.82, respectively. This suggests that the hot temperature of tea may be harmful rather than beneficial especially for the most proximal part of the stomach. In fact, a number of studies have found that hot drinks have an effect on esophageal cancer risk [27].

From a large prospective cohort study in Japan, Kinjo *et al.* showed that mortality risks of esophageal cancer was substantially associated with thermal effect of hot tea as well as alcohol drinking, smoking, and lower consumption of green–yellow vegetables [28]. It also has been shown that mate drinking and the habits of drinking 'burning hot' beverages were associated with esophagitis [29, 30]. It is not easy to distinguish the effect of the constituents in tea and the temperature at which the tea is consumed and further studies on this question is needed.

For women, a reduced risk of gastric cancer was observed even at an amount of 5 or more cups per day, which contradict previous findings in which reduced risk of gastric cancer was only observed at an intense dose such as 10 or more [31] or 7 or more cups per day [32]. In these studies, gender was not separately analyzed and information regarding anatomical subsite was also missing. It is possible that when these details are adequately considered, an amount of 5 cups or more per day may be sufficient to reduce the risk of gastric cancer.

A majority of previous case-control studies have shown a reduced risk of gastric cancer in relation to green tea consumption [24, 25, 32–36]. In both *in vitro* and animal studies, polyphenols isolated from green tea have also been shown to have antioxidant activities and the ability to inhibit nitrosation [2–4]. N-Nitroso compounds have been implicated as etiologic factors of gastric cancer and the protective effect of green tea may be due to its ability to inhibit the endogeneous formation of these nitroso compounds. Recent prospective studies however, contradict these findings [6–8]. Although it is true that case-control studies are susceptible to recall bias and the results must be interpreted cautiously, the quality of most of the case-control studies was reasonably high. They contained a sufficient number of cases, and some had population-based controls [24, 25, 31, 34, 35], appropriate adjustment including dietary factors specific for gastric cancer [31, 32, 34], and considered the anatomical subsite [24, 25]. Thus it does not seem that their findings are much less meaningful.

Green tea consumption was measured rather crudely; neither the size of a usual cup nor the strength of the tea brew was ascertained. Inaccurate measurement of green tea consumption necessarily results in random misclassification, which in turn attenuates the true association. However, such misclassification may not be so substantial as to produce a spurious positive or inverse association.

In recent years, accumulating data shows that *Helicobacter pylori* infection is closely associated with an increased risk of gastric cancer [36, 37]. Prevalence of *Helicobacter pylori* IgG antibody among randomly selected men aged 40–49 years were 76% in Ninohe (n = 131), 86% in Yokote (n = 133), and 72% in Saku (n = 118) PHC areas in our previous study in 1989–1990 [37], and its effect may not be negligible. The effect of *Helicobacter pylori* infection on the association between green tea consumption and gastric cancer risk, either as a confounding factor or interaction, may be clarified in future nested case-control studies.

We observed a statistically significant reduced risk of distal gastric cancer in women in a population-based cohort study. More prospective studies with detailed information are needed to confirm the role of green tea on the risk of gastric cancer.

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References

1. Hirohata T, Kono S (1989) Diet/nutrition and stomach cancer in Japan. *Int J Cancer* **10**: 34–36.
2. Wang ZY *et al.* (1989) . Antimutagenic activity of green tea polyphenols. *Mutat Res* **223**: 273–285.
3. Xu Y, Ho CT, Amin SG, Han C, Chung FL (1992) Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. *Cancer Res* **52**: 3875–3879.
4. Wang ZY, Hong JY, Huang MT, Reuhl KR, Conney AH, Yang CS (1992). Inhibition of N-nitrosodiethylamine-and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced tomorigenesis in A/J mice by green tea and black tea. *Cancer Res* **52**: 1943–1947.
5. Kohlmeier L, Weterings KGC, Steck S, Kok FJ (1997) Tea and cancer prevention: an evaluation of the epidemiologic literature. *Nutr Cancer* **27**: 1–13.
6. Tsubono Y *et al.* (2001) Green tea and the risk of gastric cancer in Japan. *N Engl J Med* **344**: 632–636.
7. Nagano J, Kono S, Preston DL, Mabuchi K (2001) A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). *Cancer Causes Control* **15**: 501–508.
8. Hoshiyama Y *et al.* for the Japan Collaborative Cohort Study Group (2002) A prospective study of stomach cancer death in relation to green tea consumption in Japan. *Br J Cancer* **87**: 309–313.
9. Tredaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A (1997) Tobacco smoking and gastric cancer: review and meta-analysis. *Int J Cancer* **72**: 565–573.
10. Powell J, McConkey CC (1990) Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* **62**: 440–443.
11. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF (1991) Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* **265**: 1287–1289.
12. MacDonald WC (1972) Clinical and pathologic features of adenocarcinoma of the gastric cardia. *Cancer* **29**: 724–732.
13. Yang PC, Davis S (1988) Epidemiological characteristics of adenocarcinoma of the gastric cardia and distal stomach in the United States, 1973–1982. *Int J Epidemiol* **17**: 293–297.
14. Tsugane S, Fahey MT, Sasaki S, Baba S (1999) Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. *Am J Epidemiol* **150**: 1201–1207.
15. Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S, for the JPHC Study Group (2002) Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women: the JPHC Study. *Int J Cancer* **99**: 245–251.
16. Sobue T, Yamamoto S, Watanabe S, for the JPHC Study Group (2001) Smoking and drinking habits among the JPHC Study participants at baseline survey. *J Epidemiol* **11** (Suppl): S44–S56.
17. Tsugane S, Sasaki S, Kobayashi M, Tsubono Y, Sobue T, for the JPHC Study Group (2001) Dietary habits among the JPHC Study participants at baseline survey. *J Epidemiol* **11** (Suppl): S30–S43.
18. World Health Organization (1990) *International classification of diseases for oncology*, 2nd edn. Geneva: World Health Organization.
19. Japanese Research Society for Gastric Cancer (1993) *The general rules for the gastric cancer study*, 12th edn. Tokyo: Kanehara.
20. Lauren P (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *APMIS* **64**: 31–49.
21. Rothman KJ, Greenland S (1998) *Modern Epidemiolog*, 2nd edn. Philadelphia: Lippincott-Raven Publishers.
22. SAS Institute (1996) *Changes and enhancement*: release 6.11. Cary (NC): SAS Institute Inc.
23. Sasazuki S, Sasaki S, Tsugane S, for the Japan Public Health Center Study Group (2002). Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer* **101**: 560–566.
24. Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, Jin TH (1995) Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China. *Cancer Causes Control* **6**: 532–538.
25. Ji BT, *et al.* (1996) The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer* **77**: 2449–2457.
26. Misumi A, Murakami A, Harada K, Baba K, Akagi M (1989) Definition of carcinoma of the gastric cardia. *Langenbecks Arch Chir* **374**: 221–226.
27. Cheng KK, Day NE (1996) Nutrition and esophageal cancer. *Cancer Causes Control* **7**: 33–40.
28. Kinjo Y *et al.* (1998) Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol* **8**: 235–243.
29. Munoz N, Victora CG, Crespi M, Saul C, Braga NM, Correa P (1987) Hot mate drinking and precancerous lesions of the oesophagus: an endoscopic survey in southern Brazil. *Int J Cancer* **39**: 708–709.
30. Wahrendorf J *et al.* (1989) Precursor lesions of oesophageal cancer in adolescents in a high-risk population in China. *Lancet* **ii**: 1239–1241.

31. Kono S, Ikeda M, Tokudome S, Kuratsune M (1988) A case-control study of gastric cancer and diet in Northern Kyushu, Japan. *Jpn J Cancer Res (Gann)* **79**: 1067–1074.
32. Inoue M *et al.* (1998) Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control* **9**: 209–216.
33. Tajima K, Tominaga S (1985) Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res (Gann)* **76**: 705–716.
34. Yu GP, Hsieh CC (1991) Risk factors for stomach cancer: a population-based case-control study in shanghai. *Cancer Causes Control* **2**: 169–174.
35. Setaiwan VW *et al.* (2001) Protective effect of green tea on the risks of chronic gastritis and stomach cancer. *Int J Cancer* **92**: 600–604.
36. Huang JQ, Sridhar S, Chen Y, Hunt RH (1998) Meta-analysis of the relationship between helicobacter pylori seropositivity and gastric cancer. *Gastroenterology* **114**: 1169–1179.
37. Helicobacter and Cancer Collaborative Group (2001) Gastric cancer and helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* **49**: 347–353.
38. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S (2003) Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. *J Epidemiol* 13(Suppl): **S125–133.**
39. Tsugane S, Tei Y, Takahashi T, Watanabe S, Sugano K (1994) Salty food intake and risk of Helicobacter pylori infection. *Jpn J Cancer Res* **85**: 474–478.

Tumor response to chemotherapy: The validity and reproducibility of RECIST guidelines in NSCLC patients[1]

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We investigated the validity and inter-criteria reproducibility between RECIST (Response Evaluation Criteria in Solid Tumors) guidelines and WHO (World Health Organization) criteria, considering the decrease in patient numbers resulting from inclusion of the minimum lesion size criterion introduced in RECIST guidelines. RECIST guidelines are based on unidimensional measurement and exclusion of small lesions from measurement. The aims of the study were to examine: (1) the effect of the minimum lesion size criterion, (2) the validity of unidimensional and bidimensional measurements, i.e., their relationship with tumor volume, (3) the inter-criteria reproducibility between current RECIST guidelines and previous WHO criteria. One hundred and twenty patients with non-small cell lung cancer (NSCLC) in clinical trials were evaluated. By applying the minimum lesion size criterion, six cases became ineligible without any influence on precision of tumor volume measurement. In the validity study, actual tumor volume was regarded as the gold standard. Although the unidimensional measurement had a lower correlation with tumor volume value than the bidimensional measurement, both the unidimensional measurement and bidimensional measurement correlated sufficiently well with tumor volume changes and the assessed tumor volume response. In the inter-criteria reproducibility study between RECIST guidelines and WHO criteria, the response rate assessed by RECIST guidelines (19.3%) was almost the same as that assessed by WHO criteria (20.0%). In conclusion, RECIST guidelines are adequate for evaluating tumor response to chemotherapy in terms of both validity in relation to tumor volume and inter-criteria reproducibility with the WHO criteria. (Cancer Sci 2003; 94: 1015–1020)

New guidelines for evaluating tumor response, RECIST (Response Evaluation Criteria in Solid Tumors) guidelines, have been recently adopted by many organizations.[1] RECIST guidelines stipulate the use of unidimensional measurement of lesions in contrast with the bidimensional measurement stipulated by WHO (World Health Organization) criteria[2] and define the minimum lesion size allowable for measurability of the lesion to be no less than double the slice thickness on computed tomography (CT) or magnetic resonance imaging (MRI). When this minimum lesion size is included in the eligibility criteria, the number of patients with measurable lesions decreases in comparison to previous WHO criteria, because some patients with only small lesions are excluded from the eligibility criteria.

Several previous studies have demonstrated the inter-measurement reproducibility between unidimensional and bidimensional measurement in the same cases.[1,3–5] However, they have not considered the decrease in number of eligible cases as a result of the inclusion of the minimum lesion size criterion, and thus they have been unable to demonstrate true inter-criteria reproducibility between RECIST guidelines and WHO criteria. In addition, validity has been based on the subjective theoretical inference that unidimensional measurement is more proportional to the logarithm of cell numbers than bidimensional measurement, but this hypothesis has not been objectively evaluated.[6]

Before introducing RECIST guidelines at our institution, we considered that the validity and inter-criteria reproducibility between the new and conventional criteria should be investigated. We had three objectives in investigating whether RECIST guidelines were adequate for evaluating tumor response to chemotherapy. These were to assess:

(1) The effect of the minimum lesion size criterion on the number of eligible patients and on the precision of tumor volume measurement.

(2) The validity of RECIST guidelines and WHO criteria by correlating the two different dimensional measurements with tumor volume as the gold standard, i.e. by correlating the relationship with tumor volume, and by applying the minimum lesion size criterion to these measurements.

(3) The inter-criteria reproducibility between current RECIST guidelines (unidimensional measurement in measurable cases excluding small lesions) and previous WHO criteria (bidimensional measurement in all cases including small lesions).

Materials and Methods

Patient population. This is a retrospective study of radiological findings of patients who underwent chemotherapy in clinical trials for advanced non-small cell lung cancer (NSCLC). The subjects were patients treated at the Medical Oncology Division of the National Cancer Center Hospital in Tokyo, between January 1996 and April 2000. All clinical trials were conducted according to the Helsinki Declaration and the protocol was approved by the local ethics committee. Written informed consent was obtained from each patient for each treatment protocol, which included the secondary use of treatment-associated documents. Patients were staged according to the UICC TNM Classification of malignant tumors.[7]

One hundred and twenty patients in clinical trials who fulfilled the following criteria were selected for the study:

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Abbreviations: WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; NSCLC, non-small cell lung cancer; CDDP, cisplatin; CT, computed tomography; MRI, magnetic resonance imaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence intervals.

Table 1. Patient and characteristics (all 120 cases and 50 cases analyzed by area volume)

		All	Analyzed by area volume
No. of patients		120	50
Age	Median	60	62
	Range	38–75	44–75
Sex	Male	82	35
	Female	38	15
Stage	IIIB	41	11
	IV	79	39
Histology	Adeno ca.	88	39
	Squamous cell ca.	21	8
	Adenosquamous ca.	1	1
	Large-cell ca.	10	2
Regimen	Cisplatin and paclitaxel	35	14
	Cisplatin and vindesine	26	13
	Cisplatin, docetaxel and ifosfamide	21	8
	Cisplatin and irrinotecan	12	0
	Cisplatin and docetaxel	13	9
	Cisplatin, navelbine and mitomycin	4	0
	Cisplatin, vindesine and mitomycin	3	0
	Cisplatin and gemcitabine	4	4
	Cisplatin and navelbine	2	2

1. They were histologically or cytologically diagnosed with NSCLC.
2. They were treated with cisplatin (CDDP)-based chemotherapy in clinical trials.
3. They had at least one measurable lesion.
4. They had undergone CT scans periodically for evaluating tumor response to chemotherapy prior to and at least once after treatment.

The patients' characteristics were as follows: male/female=82/38, median age=60 (range 38–75), stage III B/IV=41/79. Chemotherapy regimens are listed in Table 1.

Patients treated in daily clinical practice were considered to be unsuitable and were excluded from this study, as tumor response evaluation in the daily clinical practice of oncology is not always performed according to predefined criteria, but rather is made by subjective medical judgment based on clinical and laboratory data. In addition, tumor response evaluation is not always performed on the basis of CT examinations, and the intervals between tumor evaluations can be irregular.

Image analysis. Almost all images were acquired with a TCT-900S Superhelix (Toshiba Medical, Tokyo), with the remainder having been scanned on an X-Vigor helical CT scanner (Toshiba Medical). Helical CT was performed with fixed scanning parameters including 120 kVp, 200 mAs, table speed of 15 mm/sec (pitch, 1.5:1), 1 second per rotation and contrast agent throughout baseline and follow-up evaluations. Image reconstruction was performed at intervals of 10 mm.

We selected the unidimensional value as the longest diameter of a tumor, the bidimensional value as the product of the unidimensional value and the longest diameter perpendicular to it, the tridimensional volume value as the product of the bidimensional value and tumor height, and the area volume value as the integration of tumor area. In addition, unidimensional change, bidimensional change, tridimensional volume change, and area volume change were calculated as percentage changes in tumor size from the baseline evaluation to the follow-up evaluation. Three hundred and fifty-two evaluations were performed in 120 cases, which included 120 baseline and 232 follow-up evaluations.

Two types of CT-assisted tumor volume measurement believed to give values very close to the true tumor volume were employed and calculations were based on digitized images measured using electronic calipers (Fig.1 and Table 2). First, tridimensional volume was calculated as the product of the unidimensional value, the longest diameter perpendicular to it and tumor height. Second, area volume measurement was performed. The tumor area was measured by manually tracing the tumor outline with a computer mouse on each axial slice in which the tumor was visualized, and multiplying it by the slice thickness to yield a slice volume. The individual slice volumes were then added together to obtain an overall volume.[8]

In all 120 cases, we measured three parameters (the unidimensional value, the largest diameter perpendicular to it and the tumor height). A new computer system, which could measure tumor area on a terminal monitor, was introduced at our institution in 1999. Thus for 50 cases entering from January

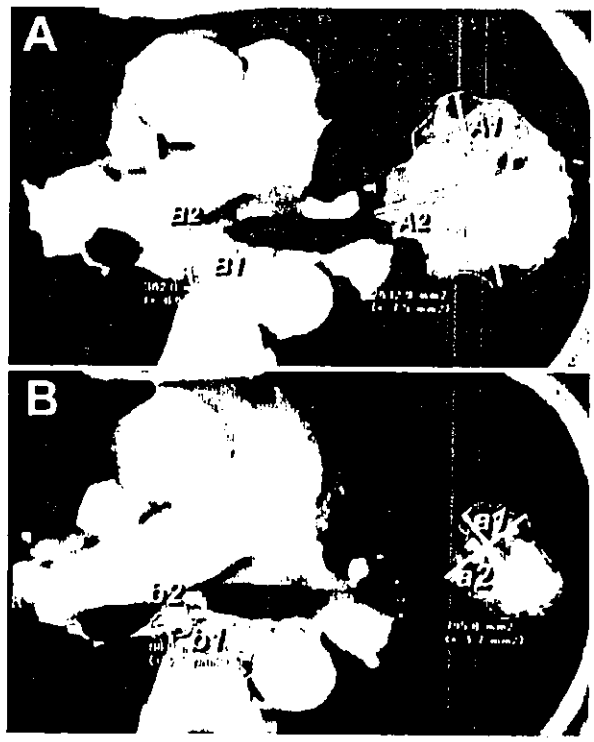

Fig. 1. Tumor measurement method: baseline evaluation (A) and follow-up evaluation (B).

1999, we were able to measure four parameters (the unidimensional value, the largest diameter perpendicular to it, the tumor height and the tumor area) in each lesion, and, as a result, the tumor volume could be more accurately calculated in these cases.

Tumors were retrospectively measured at baseline evaluation (obtained before the initiation of chemotherapy) and at regular intervals during the trials. All baseline and follow-up evaluations were retrospectively measured by the same radiologist (H.W.), who was blinded to the patient files. Lung lesions and mediastinal lesions were estimated on CT images mainly using soft tissue windows. Metastatic lesions of the abdomen and the brain were also assessed by CT examinations. If there were two or more lesions, the sum of all lesions (primary lesion, mediastinal and hilar lymphadenopathy, and metastasis lesions) up to a maximum of 5 lesions per organ and 10 lesions in total was calculated.

Tumor response evaluation. Tumor response evaluation was categorized into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) based on RECIST guidelines and WHO criteria. The RECIST PR is defined as a 30% decrease in the sum of the longest diameters and the WHO PR is defined as a 50% decrease in the sum of the products. The RECIST PD is defined as a 20% increase in the sum of the longest diameters and the WHO PD is defined as a 25% increase in the sum of the products of all lesions or in the product of any one lesion.

Each patient's tumor measurements were also evaluated according to volume criteria. If we consider spherical tumors, which grow and shrink isometrically, both the WHO 50% decrease and the RECIST 30% decrease result in a 65% tumor volume decrease. In addition, the volume change required to qualify for PD is not equivalent in the two sets of criteria. The RECIST PD (a 73% increase in tumor volume) requires a larger tumor increase than the WHO PD (a 40% increase in tumor volume).

In both criteria, a minimum interval of 4 weeks is required to confirm CR or PR. In the case of SD in RECIST guidelines, measurements must meet the SD criteria at least once after study entry at a minimum interval. In the present study, for correlation with WHO criteria, this minimum interval criterion was not applied.

The effect of minimum lesion size criteria. We examined the impact on the number of eligible patients by the minimum lesion size criterion introduced in RECIST guidelines, requiring a lesion whose minimum size is no less than double the slice thickness on images. The slice thickness was 10 mm in the present study, so the minimum lesion size was required to be no less than 20 mm at baseline evaluation before treatment and small lesions were defined as lesions less than 20 mm. The measurable cases were defined to exclude cases with only small lesions from all cases. We defined RECIST guidelines in terms of unidimensional measurement in measurable cases excluding small lesions and WHO criteria in terms of bidimensional measurement in all cases, including small lesions.

The impact of the minimum lesion size criterion on the precision of tumor volume measurements was evaluated by comparing the standard error of the correlation coefficient between measurable cases (excluding small lesions) and all cases (including small lesions).

The validity of unidimensional and bidimensional measurements, i.e. the relationship with tumor volume. To examine the validity of RECIST guidelines and WHO criteria, we estimated the Spearman's correlation coefficients between the two different dimen-

Table 2. Tumor measurement method shown in Fig. 1

	Value	Change
Unidimensional measurement	A1+B1+...	a1+b1+.../A1+B1+...
Bidimensional measurement	A1×A2+B1×B2+...	a1×a2+b1×b2+.../A1×A2+B1×B2+...
Tridimensional volume	A1×A2×A3*+B1×B2×B3+...	a1×a2×a3+b1×b2×b3+.../A1×A2×A3*+B1×B2×B3+...
Area volume	(Area A+Area B+...)×Slice thickness	Volume a+Volume b+.../Volume A+Volume B+...

* A3: tumor height.

Table 3. Validity (Tridimensional volume measurement)

	Value			Change			Response rate		
	Uni	Bi	Evaluations	Uni	Bi	Evaluations	Uni	Bi	Volume
Measurable 114 cases	0.85 (0.018)*	0.97 (0.005)*	336	0.9 (0.02)*	0.95 (0.010)*	222	19.30% (12.5–27.7)**	21.10% (14.0–29.7)**	19.30% (12.5–27.7)**
All 120 cases	0.84 (0.019)*	0.97 (0.005)*	352	0.9 (0.016)*	0.94 (0.011)*	232	19.20% (12.6–27.4)**	20.00% (13.3–28.3)**	19.20% (12.6–27.4)**

* Spearman's correlation coefficient (standard error).
** The response rate (95% confidence intervals).
Abbreviations: Uni represents the unidimensional measurement; Bi represents the bidimensional measurement.

Table 4. Validity (Area volume measurement)

	Value			Change			Response rate		
	Uni	Bi	Evaluations	Uni	Bi	Evaluations	Uni	Bi	Volume
Measurable 46 cases	0.8 (0.040)*	0.92 (0.019)*	133	0.84 (0.036)*	0.85 (0.038)*	87	19.60% (9.4–39.9)**	19.60% (9.4–39.9)**	17.40% (7.8–31.4)**
All 50 cases	0.8 (0.038)*	0.93 (0.017)*	144	0.83 (0.032)*	0.81 (0.044)*	94	18.00% (8.5–31.4)**	18.00% (8.5–31.4)**	16.00% (7.2–29.1)**

* Spearman's correlation coefficient (standard error).
** The response rate (95% confidence intervals).
Abbreviations: Uni represents the unidimensional measurement; Bi represents the bidimensional measurement.

sional values (unidimensional measurement and bidimensional measurement) and the gold standard value (tridimensional volume measurement and area volume measurement). We also estimated the Spearman's correlation coefficient between the two different dimensional changes and the gold standard changes. Furthermore, we compared tumor responses assessed by using the two different dimensional criteria with those using the gold standard criteria.

The inter-criteria reproducibility between RECIST guidelines and WHO criteria. To examine the inter-criteria reproducibility between RECIST guidelines and WHO criteria, the tumor responses assessed by applying the two criteria were divided into four categories which represented CR, PR, SD and PD. We examined whether the response rate would change as a result of unidimensional measurement or application of the minimum lesion size criterion.

All analyses were conducted with SAS ver.8.02 (SAS Institute, Cary, NC).

Results

The effect of the minimum lesion size criterion. When the minimum lesion size criterion for measurable lesions introduced in RECIST guidelines was applied, six cases (5%) out of 120 cases turned out to have no measurable lesions and were considered ineligible for tumor response evaluation. The number of eligible cases thus decreased from 120 to 114. Additionally, in 40 of these 114 cases, the number of measurable lesions decreased. There was no influence on the number of measurable lesions in 74 cases.

We also examined the effect on the precision of tumor volume measurements when the minimum lesion size criterion in RECIST guidelines was applied and found that the standard error of the correlation coefficient between measurable cases (excluding small lesions) and all cases (including small lesions) was almost the same (Tables 3 and 4).

The validity of unidimensional and bidimensional measurements, i.e. the relationship with tumor volume. In the validity examinations, the two types of CT-assisted tumor volume measurement (tridimensional volume measurement and area volume measurement) were regarded as the gold standard. Table 3 shows Spearman's correlation coefficient and the standard error for each evaluation. The response rate for each evaluation is also shown in Table 3.

The unidimensional value had a lower correlation with the tridimensional volume value than the bidimensional value (Figs. 2 and 3). However, as regards the correlation with the tridimensional volume change, unidimensional change exhibited no difference from bidimensional change. In measurable cases excluding small lesions, the response rates were 19.3% (95% CI (confidence intervals): 12.5–27.7%) (22/114) for unidimensional measurement (RECIST guidelines) and 19.3% (95% CI: 12.5–27.7%) (22/114) for tridimensional volume measurement. In all cases including small lesions, the response rates were 20.0% (95% CI: 13.3–28.3%) (24/120) for bidimensional measurement (WHO criteria) and 19.2% (95% CI: 12.6–27.4%) (23/120) for tridimensional volume measurement. The response rates among unidimensional measurement, bidimensional measurement and tridimensional volume measurement were almost the same.

Area volume measurement showed the same tendency as the tridimensional volume measurement (Table 4). Unidimensional value had a lower correlation with the area volume value than bidimensional value. In terms of the correlation with area vol-

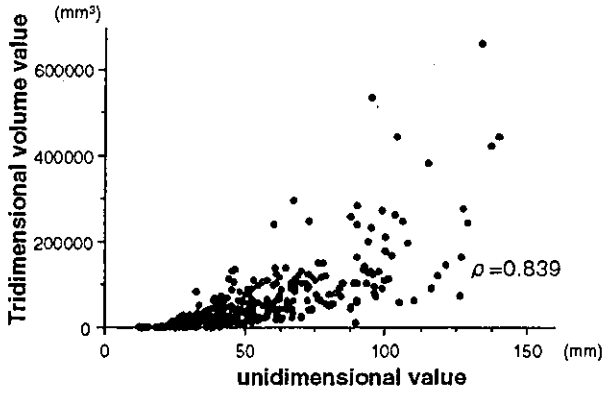

Fig. 2. Validity: Correlation between unidimensional value and tridimensional volume value in all 120 cases (352 evaluations).

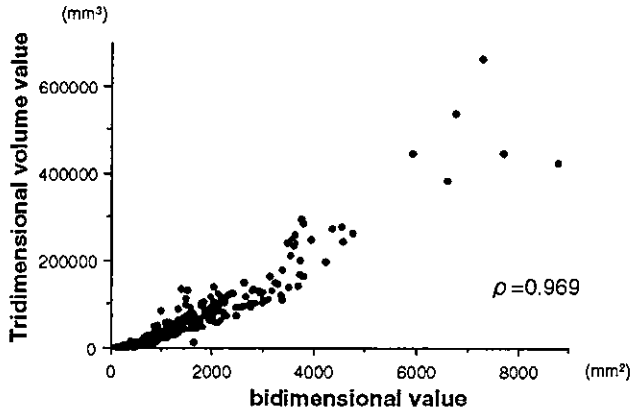

Fig. 3. Validity: Correlation between bidimensional value and tridimensional volume value in all 120 cases (352 evaluations).

Table 5. Inter-criteria reproducibility (Comparison of tumor response evaluations)

A. Unidimensional measurement

	CR	PR	SD	PD	Ineligible	Response rate
Measurable cases (RECIST)	0	22	77	15	6	19.3% (22/114)
All cases	0	23	82	15	0	19.2% (23/120)

B. Bidimensional measurement

	CR	PR	SD	PD	Ineligible	Response rate
Measurable cases	0	24	71	19	6	21.1% (24/114)
All cases (WHO)	0	24	75	21	0	20.0% (24/120)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

ume change, however, unidimensional change showed no difference from bidimensional change. In measurable cases excluding small lesions, the response rates were 19.6% (95% CI: 9.4–33.9%) (9/46) for unidimensional measurement (RECIST guidelines) and 17.4% (95% CI: 7.8–31.4%) (8/46) for area volume measurement. In all cases including small lesions, the response rates were 18.0% (95% CI: 8.5–31.4%) (9/50) for bidimensional measurement (WHO criteria) and 16.0% (95% CI: 7.2–29.1%) (8/50) for area volume measurement. Thus, the response rates among unidimensional measurement, bidimensional measurement and area volume measurement were almost the same.

The inter-criteria reproducibility between RECIST guidelines and WHO criteria. In the inter-criteria reproducibility examination, the response rates based on RECIST guidelines and WHO criteria were evaluated (Table 5). In the unidimensional measurement, the best response (measurable cases/all cases) was CR 0/0, PR 22/23, SD 77/82, and PD 15/15, while the response rates were 19.3% (95% CI: 12.5–27.7%) (22/114) for measurable cases and 19.2% (95% CI: 12.5–27.4%) (23/120) for all cases. In the bidimensional measurement, the best response (measurable cases/all cases) was CR 0/0, PR 24/24, SD 71/75, and PD 19/21, while the response rates were 21.1% (95% CI: 14.0–29.7%) (24/114) for measurable cases and 20.0% (95% CI: 13.3–28.3%) (24/120) for all cases. Thus, the response rate was almost the same for RECIST guidelines and WHO criteria at 19.3% and 20.0%, respectively.

Unidimensional value and bidimensional value also correlated well (all cases 0.91/measurable cases 0.92), as did unidimensional change and bidimensional change (all cases 0.93/measurable cases 0.93).

Eleven patients developed new lesions. Four cases were assessed as PD by RECIST guidelines but six cases were assessed as PD by the WHO criteria due to an increase in the sum of all pre-existing lesions. In addition, four cases were assessed as PD by the WHO criteria due to an increase in any one pre-existing lesion. Thus, in total, 15 cases were assessed as PD by RECIST guidelines (unidimensional measurement in measurable cases) and 21 cases by the WHO criteria (bidimensional measurement in all cases).

Discussion

To our knowledge, this is the first statistical analysis of actual measurements that can clearly show the validity and inter-criteria reproducibility between RECIST guidelines and WHO criteria, considering the decrease in patient numbers resulting from inclusion of the minimum lesion size criterion.

When the minimum lesion size criterion was applied, the eligible cases changed from 120 to 114 (95%) cases. Thus, we had to try to recruit 127 cases in total to evaluate 120 eligible cases, i.e., 7 cases (5.8%) more than previously needed had to be recruited.

The minimum lesion size criterion, i.e., evaluation of only measurable lesions excluding small lesions, could not be considered to have any influence on the precision of tumor volume measurement. However, the role of the minimum lesion size may require further examination (for example, by considering inter-observer reproducibility).

In the validity study, actual tumor volume was regarded as the gold standard. Although the unidimensional measurement had a lower correlation with tumor volume value than the bidimensional measurement, both the unidimensional measurement and bidimensional measurement correlated sufficiently well with tumor volume changes and the assessed tumor volume response. These results led to the conclusion that both RECIST guidelines and WHO criteria were valid in relation to tumor volume.

In the inter-criteria reproducibility study between RECIST guidelines and WHO criteria, the response rate assessed by applying RECIST guidelines (19.3%) was almost the same as that assessed by applying WHO criteria (20.0%). These results led to the conclusion that there was sufficient inter-criteria reproducibility between RECIST guidelines and WHO criteria.

The bidimensional value offers advantages in assessment of tumor volume over the unidimensional value because it has the potential to provide a more accurate description of tumor volume. However, the differences resulting from the measurement method are not large enough to alter assessed tumor change or to affect the categorization of tumor response. In terms of tumor response classification into only four categories (CR, PR, SD, PD), the response rates obtained by all measurements showed a high agreement. This is why RECIST guidelines using only simple unidimensional measurement are adequate for accurately evaluating tumor response to chemotherapy.

In this study, there were more WHO PD cases (21 cases) than RECIST PD cases (15 cases) because of the differences in definition of PD in the two sets of criteria. Two cases were assessed as PD by the WHO criteria, but not by RECIST guidelines due to increases in all lesions (a 40% increase vs. a 73% increase in tumor volume). In addition, four cases were assessed as PD by the WHO criteria due to increases in any one lesion, although other target lesions had not progressed and tumor response evaluation could be assessed SD by RECIST guidelines based on the sum of the products of all lesions. This was a common problem with the WHO criteria.

CT-assisted tumor volume calculations with helical CT are likely to provide the most precise measurements when assessing irregularly shaped structures which exhibit non-uniform size changes. Simple tridimensional volume measurements can be as accurate as area volume measurements.[9,10] This was reflected in our study, in which tridimensional volume measurements and area volume measurements were highly correlated (all cases 0.98/measurable cases 0.97).

However, the present study had several weaknesses and some further investigation is needed. First, nontarget lesions could not be accurately evaluated in this study because it is retrospective. However, as there was no CR in the target lesions, the best overall response was not influenced and the same conclusions could be reached without the evaluation of nontarget lesions. Second, the observer was a single radiologist (H.W.), so the influence of inter-observer reproducibility and intra-observer reproducibility could not be examined. Third, tumor volume was regarded as the gold standard and as a surrogate for survival. As the true gold standard is survival, further studies to correlate tumor response with survival are needed in larger trials. Fourth, our slice thickness was 10 mm, and therefore 20 mm were defined as minimum lesion size. However, RECIST guidelines allow for a minimum lesion size of 10 mm if measurements are made with a slice thickness of 5 mm with helical CT. The multidetector-row CT system, which can create a thinner slice thickness, is a recent development in routine clinical practice. The outcomes for currently ineligible patients when applying the thinner slice thickness should be evaluated in a further study.

We conclude that RECIST guidelines are adequate for evaluating tumor response to chemotherapy, both in relation to tumor volume and inter-criteria reproducibility with the WHO criteria. Thus, the present study serves to support and strengthen the simplification and standardization of tumor response evaluation to chemotherapy offered by the RECIST guidelines.

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1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**: 205–16.
2. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
3. Sohaib SA, Turner B, Hanson JA, Farquharson M, Oliver RT, Reznek RH. CT assessment of tumour response to treatment: comparison of linear, cross-sectional and volumetric measures of tumour size. *Br J Radiol* 2000; **73**: 1178–84.
4. Werner-Wasik M, Xiao Y, Pequignot E, Curran WJ, Hauck W. Assessment of lung cancer response after nonoperative therapy: tumor diameter, bidimensional product, and volume. A serial CT scan-based study. *Int J Radiat Oncol Biol Phys* 2001; **51**: 56–61.
5. Warren KE, Patronas N, Aikin AA, Albert PS, Balis FM. Comparison of one-, two-, and three-dimensional measurements of childhood brain tumors. *J Natl Cancer Inst* 2001; **93**: 1401–5.
6. James K, Eisenhauer E, Christian M, Terenziani M, Vena D, Muldal A, Therasse P. Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999; **91**: 523–8.
7. Sobin LH, Wittekind Ch., editors. UICC TNM Classification of malignant tumours. 5th ed. New York: John Wiley & Sons Inc; 1997.
8. Breiman RS, Beck JW, Korobkin M, Glenny R, Akwari OE, Heaston DK, Moore AV, Ram PC. Volume determinations using computed tomography. *Am J Roentgenol* 1982; **138**: 329–33.
9. Van Hoe L, Van Cutsem E, Vergote I, Baert AL, Bellon E, Dupont P, Marchal G. Size quantification of liver metastases in patients undergoing cancer treatment: reproducibility of one-, two-, and three-dimensional measurements determined with spiral CT. *Radiology* 1997; **202**: 671–5.
10. Bozcuk HS, Ravi R, Turner B, Tsetis D, Thomas JM, Chan O, Reznek R, Hendry WF, Oliver RT. Computed tomography 21 days after chemotherapy, three-dimensional estimates of metastatic volume and the need for surgery in patients with germ cell cancer. *BJU Int* 2000; **86**: 707–13.

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Phase II Study of Sequential Methotrexate and 5-Fluorouracil Chemotherapy Against Peritoneally Disseminated Gastric Cancer with Malignant Ascites: a Report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial

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Background: The efficacy of systemic chemotherapy against peritoneal dissemination from advanced gastric cancer (AGC) remains unclear, because the peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies. In this study, we evaluated the efficacy and toxicity of sequential MTX and 5FU therapy (MF) in chemotherapy-naive patients with AGC accompanied by malignant ascites in a phase II setting.
Methods: The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 every 6 h, for a total of six times) was commenced 24 h after MTX administration.
Results: Thirty-seven chemotherapy-naive patients with AGC presenting with malignant ascites were enrolled in this trial. The median age was 60 years (range, 25–74 years) and most patients (86%) had a performance status of 0–1. In total, 355 administrations of the sequential MTX/5FU therapy were performed. Major toxicity consisted of myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia occurred in 10.8% of the patients. The overall objective response rate was 5.7% (two partial responses in 35 patients; 95% confidence interval: 0.7–19.2%). However, the response rate of ascites was 35.1% (complete disappearance in three patients and apparent decrease in 10 patients; 95% confidence interval: 20.2–52.5%).
Conclusions: Sequential MTX/5FU therapy is effective against AGC with malignant ascites with acceptable toxicity and warrants further investigations in a phase III setting.

Key words: sequential MTX/5FU chemotherapy – gastric cancer, peritoneal dissemination – ascites – clinical trial

INTRODUCTION

Despite a declining incidence in many industrial countries, gastric cancer remains one of the most common malignancies globally. Although this tumor is potentially curable with surgery when diagnosed at an early stage, the prognosis for patients with unresectable or metastatic disease is very poor, with a median survival of 3–4 months when they receive the best supportive care without palliative surgery or chemotherapy (1–3). Gastric cancer can progress to systemic disease through various routes such as direct invasion or lymphatic or vascular spread. Peritoneal dissemination, i.e. peritoneal carcinomatosis, which occurs mainly as a result of direct invasion and/or lymphatic spread, is very common in advanced gastric cancer and is considered an incurable disease state (4). Peritoneal dissemination may cause serious complications, such as

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intestinal obstruction, massive ascites and hydronephrosis associated with the clinical presentation of abdominal pain and fullness, vomiting, constipation, malnutrition and renal dysfunction. From the clinical point of view, palliative management of those complications warrants special considerations and represents a therapeutic challenge in oncology (5,6). Although the major treatment option for unresectable or metastatic gastric cancer is systemic chemotherapy, this strategy has been generally believed to have little effect on peritoneal dissemination, because the drugs could not be delivered sufficiently through the peritoneum–plasma barrier to the disseminated tumor cells (7). However, the efficacy of systemic chemotherapy against peritoneal dissemination from gastric cancer remains unclear, because peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies and therefore few reports are available about the efficacy of systemic chemotherapy against peritoneal dissemination. 5-Fluorouracil (5FU) remains the mainstay for chemotherapy against gastric cancer and a variety of drugs have been tested as modulators to increase its chemotherapeutic efficacy. The modulators that have been most widely used in clinical practice against gastrointestinal tract cancers are folinic acid (leucovorin) and methotrexate (MTX) (8,9). MTX enhances 5FU cytotoxicity via DNA and/or RNA synthesis inhibition when the two drugs are administered in sequence, with 5FU administered a few hours after MTX (10,11). A meta-analysis of randomized trials of sequential MTX/5FU therapy revealed a higher response rate than for single agent bolus 5FU in colorectal cancer (12). The toxicity of these sequential MTX/5FU regimens was comparable to that of 5FU alone (i.e. vomiting, stomatitis, diarrhea and leukopenia). The sequential MTX/5FU therapy was found in phase II trials for advanced gastric cancer to have antitumor activity against advanced gastric cancer (13,14). A Japanese phase II trial of sequential MTX/5FU therapy against advanced gastric cancer demonstrated that low- and intermediate-dose MTX regimens achieved response rates of 23% (13 PRs/56 patients) and 41% (15 PRs/37 patients), respectively (15). Sequential MTX/5FU therapy is widely used as one of the standard treatment regimens for patients with unresectable or metastatic gastric cancer at present in Japan. Konishi et al. reported that sequential MTX/5FU therapy was effective in patients with peritoneal dissemination with a response rate of 23% (6/26) and that ascites disappeared in eight of 16 patients (50%) treated with this therapy (16). Those findings suggest that sequential MTX/5FU might be effective in advanced gastric cancer with peritoneal dissemination.

The objective of this study was to evaluate the efficacy and toxicity of sequential MTX/5FU chemotherapy in advanced gastric cancer with malignant ascites in order to determine whether this regimen is worthy of further investigation in a phase III trial for the treatment of patients with peritoneal dissemination from advanced gastric cancer. The primary endpoints planned for this study were tumor response rate and response rate in ascites. Secondary endpoints were overall survival and toxicity. To our knowledge, there has been no prior study that evaluated the efficacy and toxicity of systemic chemotherapy in a phase II setting in patients with advanced gastric cancer who have peritoneal dissemination with malignant ascites.

SUBJECTS AND METHODS

Eligibility

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histologically confirmed gastric cancer; (2) unresectable or recurrent disease; (3) peritoneal dissemination with cytologically confirmed malignant ascites evaluable by CT scan or ultrasonography; (4) measurable or evaluable disease; (5) age 20–75 years; (6) performance status (PS) ≤2 on Eastern Cooperative Oncology Group (ECOG) scale; (7) no prior chemotherapy with the exception of one adjuvant chemotherapy; (8) adequate bone marrow function (WBC ≥4000/mm^3 and platelets ≥100 000/mm^3) (9) adequate liver function (serum bilirubin level ≤2.0 mg/dl and serum transaminase level ≤2.5-fold the upper limit of normal; (10) adequate renal function (serum creatinine and blood urea nitrogen within the upper limit of normal; (11) serum albumin ≥2.6 g/dl; (12) normal ECG; (13) currently hospitalized; (14) life expectancy at least 8 weeks; (15) written informed consent. Patients with active bleeding from the gastrointestinal tract, other active synchronous carcinoma, central nerve metastasis or concurrent uncontrolled medical illness and pregnant or lactating women were excluded. Patients with massive ascites that required drainage for the relief of symptoms were also excluded. The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center.

Treatment Plan

The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 orally or i.v. every 6 h, six times) was commenced 24 h after MTX administration. To prevent toxicity from MTX, acetazolamide (250 mg) was given intravenously immediately after the infusion of MTX and sodium bicarbonate (33.3 mequiv.) added to 500 ml of electrolyte solution was administered by drip infusion for urine alkalinization during the 3 h interval between the administration of MTX and 5FU. The plasma level of MTX was monitored 24 h after MTX administration and leucovorin rescue at 10 mg/m^2 was administered every 6 h until the plasma level of MTX was $<1 \times 10^{-6}$ mol/l. At the time of each administration, patients were required to fulfill the following criteria: leukocyte count ≥3000/ mm^3; platelet count ≥75 000/ mm^3; adequate liver and renal function as eligibility criteria; PS 0–2; and absence of toxicity grade 2 or greater. The treatment was repeated unless disease progression or severe toxicity was observed. The treatment was terminated when the ascites did

Table 1. Patients' characteristics

Characteristic	Total (n = 37)
Gender	
Male	21
Female	16
Age (years)	
Median	60
Range	25–74
ECOG performance status score	
0	8
1	24
2	5
Histological type	
Intestinal type	
Well-differentiated tubular adenocarcinoma	4
Moderately differentiated tubular adenocarcinoma	7
Papillary adenocarcinoma	1
Diffuse type	
Poorly differentiated adenocarcinoma	6
Mucinous adenocarcinoma	2
Signet-ring cell carcinoma	17
Macroscopic type of primary tumor	
Scirrhous type	21
Non-scirrhous type	16
Metastatic sites	
Lymph nodes	25
Liver	7
Krukenberg's tumor	2
Douglas's metastasis	1
Lung	2
Bone	1
Pleural effusion	4

not improve within 8 weeks or when toxicity did not disappear within 6 weeks.

Response and Toxicity Evaluation

Tumor response was assessed by CT scan or ultrasonography of the target lesions every 4 weeks after the first administration of MTX. Complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were defined according to the response assessment criteria proposed by the Japanese Research Society for Gastric Cancer (17). The response in ascites was evaluated by abdominal CT scan or ultrasonography based on the following specific criteria used in this study: (1) disappearance of ascites – disappearance of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (2) decrease of ascites – apparent decrease of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (3) no response of ascites – no change of ascites volume visualized by CT scan or ultrasonography. The data for tumor response in all responders was confirmed by an extramural review. The toxicity was evaluated according to the JCOG common toxicity criteria (18).

Statistical Analysis

The sample size was determined based on the precision of the estimates. The efficacy for malignant ascites was expected to be 30%. Fifty subjects and an observed efficacy of 30% would provide a 95% confidence interval of 17.9–44.6% or width of 26.7%. The expected accrual period was 1.5 years. Interim analysis was planned to test for inefficacy of the treatment by examining whether a 90% upper confidence bound of efficacy would exceed 25% for first 20–25 patients. The overall survival was calculated for the period from the date of registration to the date of death. Overall survival was calculated by the Kaplan–Meier method and confidence intervals were calculated based on Greenwood's formula.

RESULTS

Patient Population and Study Treatment

Between February 1997 and October 1999, 37 patients were enrolled in this trial from nine out of 13 participating institutions. Although this study was originally planned as a phase II study in which 50 patients would be enrolled within 1.5 years of the start of the study, the patient enrollment was delayed and was finally terminated before the projected number of patients had been achieved based on the decision of the JCOG monitoring committee that the evaluation of efficacy and toxicity was possible even with only 37 enrolled patients. Table 1 lists the demographic data, baseline disease and pretreatment characteristics of all patients. Twenty-one males and 16 females were registered as receiving first-line chemotherapy. The median age of the patients was 60 years (range, 25–74 years) and the majority of the patients (86%) had a good performance status of 0–1. Twenty-one patients (57%) had macroscopically scirrhous-type advanced gastric cancer. Twenty-five patients had histologically diffuse types (six poorly differentiated adenocarcinoma, two mucinous carcinoma and 17 signet-ring cell carcinoma). Two patients had undergone surgery prior to enrollment in this trial (one palliative total gastrectomy and the other exploratory laparotomy resulting in no resection). One patient suffered from hemilateral hydronephrosis due to peritoneal dissemination with normal range of renal function tests.

In total, 355 administrations of the sequential MTX/5FU therapy were performed in 37 patients. The median number of administrations was eight (range, 1–42). Twenty-nine of 37 enrolled patients (78%) received at least four administrations of the sequential MTX/5FU therapy. All patients were assessable for toxicity and response of ascites to chemotherapy. Thirty-five patients were assessable for objective tumor

Table 2. Toxicity profiles

Toxicity	JCOG grade					Grade 4 (%)
	0	1	2	3	4	
Hematological toxicity						
Leukopenia	11	13	7	4	2	5.4
Neutropenia	17	5	5	6	4	10.8
Anemia	7	6	15	9	–	–
Thrombocytopenia	32	3	1	1	0	0
Non-hematological toxicity						
Nausea/vomiting	13	14	10	0	–	–
Diarrhea	25	4	6	2	0	0
Stomatitis	30	7	0	0	0	0
Alopecia	35	2	0	–	–	–
Allergic reaction	36	1	0	0	0	0
Fever	18	10	9	0	0	0
Peripheral neuropathy	36	1	0	0	–	–
Total bilirubin	20	–	8	8	1	2.7
AST	16	16	5	0	0	0
ALT	16	16	5	0	0	0
Alkaline phosphatase	16	17	2	2	0	0
Creatinine	33	2	0	2	0	0
Hyponatremia	12	17	7	0	1	2.7
Hypokalemia	21	12	4	0	0	0

response to chemotherapy. The most frequent reason for treatment termination was disease progression (27 patients, 73%). Other reasons for treatment termination were no response after 8 weeks from initiation of treatment in two, patient refusal in two, severe toxicity in two, death in three (one due to disease progression and two treatment-related) and medical judgment by the investigators in one.

Toxicity

The toxicity observed in the study period is summarized in Table 2. The major toxicity was myelosuppression and gastrointestinal toxicity. Grades 3 and 4 neutropenia occurred in 16 and 11% of the patients, respectively. Severe thrombocytopenia was infrequent. The incidence of grade 3 diarrhea was 5%. Mild nausea and vomiting (grades 1 and 2) were frequently experienced (65%). An increase in total bilirubin of grade 4 was observed in one patient (2.7%) and was diagnosed as obstructive jaundice caused by the development of lymphadenopathy from the primary disease. An increase in total bilirubin grade 3 was observed in eight patients, three cases of which were judged to be treatment-related. An increase in serum creatinine grade 3 was observed in two patients (5.4%). One patient experienced grade 4 hyponatremia due to loss of oral intake associated with primary disease. Early death, which was defined as death within 30 days from the last administration of anti-cancer drugs, occurred in five patients. The causal relationship between the death and the study treatment was 'unlikely' in three of those five patients. However, the remaining two deaths were assessed to be treatment-related. One patient died of severe neutropenia and rapidly progressive disseminated intravascular coagulation (DIC), which was complicated with respiratory dysfunction, and the other patient died of progressive neutropenic sepsis.

Efficacy

The efficacy-related data are summarized in Table 3. Only two of 35 response-assessable patients achieved objective partial response (response rate 5.7%; 95% confidence interval: 0.7–19.2%). However, in terms of the response of ascites, three disappearances and 10 decreases of ascites were obtained (response rate 35.1%; 95% confidence interval: 20.2–52.5%). The median duration of response of ascites was 103 days with a range of 52–337 days. The median survival time of all patients was 155 days (95% confidence interval: 131–225 days) and the 1 year survival rate was 16.2% (95% confidence interval: 4.3–28.1%).

DISCUSSION

Although unresectable or metastatic gastric cancer is potentially incurable, there is significant evidence that adding systemic chemotherapy to the best supportive care could provide benefits in survival and quality of life as compared with best supportive care alone (1–3). However, it has been difficult to assess which of many available regimens is the most effective, although several regimens have been tested in randomized controlled trials. Some randomized trials failed to demonstrate the superiority of 5FU-based combination regimens as compared with 5FU-monotherapy (19–21). A recent randomized controlled trial showed that three commonly used combination regimens, 5FU/adriamycin/MTX (FAMTX), 5FU/cisplatin (FP) and etoposide/leucovorin/5FU (ELF), have only modest activity and that there were no significant differences in overall survival among these regimens (22). More recently, infusional 5FU in combination with cisplatin and epirubicin (ECF) showed significant superiority over FAMTX in terms of response rate, quality of life and survival, suggesting that the ECF could be a new standard treatment for future clinical trials (23). However, regarding the median survival time in those large-scale trials, there was little substantial difference among the various regimens. Therefore, in general, 5FU-based or cisplatin-based combinations are widely accepted as a possible standard therapy (24). In clinical practice, oncologists need to select a regimen considered to be the most appropriate for each individual patient based on the medical condition of each patient, including such factors as age, performance status, organ function and extent of disease. The cisplatin-based regimens are usually inappropriate to be used for patients having peritoneal dissemination and retention of ascites, because such patients have potential renal impairment or poor performance

Table 3. Responses to treatment (total of 355 administrations of the sequential MTX/5FU therapy)

	No. of evaluable patients	CR	PR	NC	PD	NE	Response rate (%)	95% CI (%)
Objective response	35	–	2	21	6	6	5.7	0.7–19.2
Response in ascites	37	3	10	15	6	3	35.1	20.2–52.5

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

status, which makes it difficult to tolerate the large volume hydration for the prevention of cisplatin-induced renal injury. Among several 5FU-based regimens, sequential MTX/5FU therapy is widely used because this regimen has definite anti-tumor activity against advanced gastric cancer with acceptable toxicity even in high-risk patients. The purpose of the present phase II study was to evaluate the efficacy and toxicity of the sequential MTX/5FU regimen in patients with unresectable gastric cancer with peritoneal dissemination accompanied by malignant ascites and to assess whether further investigation in a phase III setting is warranted.

Progression to peritoneal dissemination is very common in advanced gastric cancer and is frequently a component of the first episode of failure after surgery for primary gastric cancer (25). Therefore, intraperitoneal chemotherapy has previously been investigated for peritoneal dissemination for the purposes of palliation and the prevention of peritoneal metastasis after surgery in high-risk patients. The pharmacokinetic rationale for intraperitoneal therapy is that drug concentrations within the peritoneal cavity are several-fold to 1–2 logs higher than concentrations that can be achieved after oral or intravenous treatment (26,27). In ovarian cancer, a large randomized trial demonstrated a small but statistically and clinically significant survival advantage in patients receiving intraperitoneal therapy (28). However, generally the efficacy of intraperitoneal chemotherapy is considered to be modest because the penetration of intraperitoneally injected drug into submesothelial tissue is too limited to achieve anti-tumor activity. Moreover, intraperitoneal chemotherapy sometimes induces systemic adverse events similar to systemic chemotherapy in addition to local complications such as chemical peritonitis. No definite data are currently available to specify which treatment option, intraperitoneal or systemic chemotherapy, is more suitable for patients with peritoneal dissemination in terms of benefit regarding survival and quality of life.

When we perform systemic chemotherapy in patients who have fluid retention such as ascites or pleural effusion, we have to consider the pharmacokinetic alterations of the anti-tumor agents administered. Intravenously administered MTX penetrates the ascites or pleural effusion and the clearance rate of MTX from ascites and plasma is ~5 and ~120 ml/min, respectively (29). Therefore, the retention of body fluid prolongs the terminal plasma half-life of intravenously administered drug owing to the slow re-entry of the sequestered drug into the bloodstream. Such phenomena should be associated with both favorable anti-tumor activity against peritoneal or pleural dissemination and with the potential risk of systemic toxicity. In another phase II study of sequential MTX/5FU therapy against unresectable or metastatic gastric cancer previously conducted by the JCOG, in which the same dosage and schedule as in the present study were utilized but the patients having ascites were ineligible for entry (JCOG 9207 study), none of 56 enrolled patients experienced grade 3 or 4 neutropenia (data not shown). In the present study, grades 3 and 4 neutropenia were observed in six (16 %) and two patients (11 %), respectively. The incidence of leukopenia, anemia, increase in total bilirubin and increase in serum creatinine of grade 3 or 4 tended to be more frequent in the present study than in the JCOG 9207 study (data not shown). Therefore, the toxicity of the sequential MTX/5FU therapy might be more severe in patients with malignant ascites than in those without. Two treatment-related deaths were observed in the present study. These two patients developed progressive neutropenic sepsis, which is a major cause of death. Although these two patients had met the eligibility criteria required in the study, both patients were retrospectively shown to be at high-risk for neutropenic infection, because pretreatment serum CRP values were highly elevated in both patients and leukocytosis was also observed at the baseline in one patient. Therefore, we consider that patients with apparent inflammatory signs such as elevation of CRP or leukocytosis should be excluded from future studies to prevent neutropenic sepsis. It is known that the different methods of administration of 5FU, either as a bolus or by infusion, represent different efficacy and toxicity profiles, thus infusional 5FU has more clinical benefit in efficacy (response rate) and safety in metastatic colorectal cancer. At present, however, we do not have sufficient data to establish whether these clinical observations hold true in patients with peritoneal dissemination with malignant ascites and it seems to be important to investigate the infusional 5FU-based regimens in this clinical setting, which may contribute to reducing the toxicity.

It is difficult to evaluate the efficacy of chemotherapy against peritoneal dissemination in clinical trials as well as in clinical practice, because most disseminated tumor cells do not form a measurable mass but rather constitute a diffuse lesion. Clinicians have to assess the efficacy of treatment and disease status in each patient based on the integration of clinical information such as clinical imaging, tumor markers and clinical symptoms. In the present study, the therapeutic efficacy was assessed according to the specific criteria for the study based on the change in the volume of ascites visualized by abdominal CT scan or ultrasonography as a surrogate marker. Using these criteria, we found that the ascites disappeared or was decreased by the MTX/5FU therapy in 35% of the patients. Konishi et al.

also reported that ascites disappeared in 50% (8/16) of patients with peritoneal-disseminated gastric cancer after MTX/5FU therapy (16). These results show that sequential MTX/5FU therapy is effective in controlling malignant ascites and also suggest that this regimen is effective against peritoneal dissemination from advanced gastric cancer.

Although the present study was originally planned as a phase II study involving 50 patients, patient enrollment had been delayed and finally terminated before the projected number of patients was achieved. The delay in patient enrollment was probably caused by the eligibility criteria for this study. Although peritoneal dissemination of advanced gastric cancer is very common in clinical practice, most patients with peritoneal dissemination accompanied by malignant ascites tend to have relatively poor performance status and impaired organ function, which was considered to be a critical issue delaying patient enrollment. The JCOG monitoring committee accepted the investigators' decision that the objectives of this study, which were to calculate the response rate in ascites and to evaluate the safety of sequential MTX/5FU therapy for decision-making to pursue further investigation in a phase III study, were achieved even with the actual sample size of 37 patients and that the response rate in ascites of 35% (95% confidence interval: 20.2–52.5%) observed in this study was positive.

It is well known that peritoneal dissemination of gastric adenocarcinoma occurs more commonly as the histologically diffuse type than the intestinal type. Konishi et al. reported that sequential MTX/5FU therapy was more effective against undifferentiated gastric cancer (i.e. histologically diffuse type) than differentiated gastric cancer (i.e. histologically intestinal type), with a response rate of 32% (9 PRs/28 patients) vs 0% (0 PRs/10 patients) (16). A similar tendency was observed in the present study, namely that the response rate of ascites was higher for the histologically diffuse type than for the intestinal type (44%, 11 responders among 25 patients, versus 17%, two responders among 12 patients). The difference in the efficacy of the sequential MTX/5FU therapy depending on the histological type might be explained by the difference in the activities of two enzymes, thymidylate synthetase and thymidine kinase, in the various histological types of gastric cancer (30). However, other reports have suggested that there were no significant differences according to the histological type. (15)

In conclusion, the findings of the present study suggest that sequential MTX/5FU therapy is effective in controlling malignant ascites from gastric cancer with overall acceptable toxicity and that further investigations are warranted. However, the present study also suggests that severe toxicity may occur more frequently in patients with malignant ascites than in those without malignant ascites. Whether there is true clinical benefit in this regimen for patients with peritoneal dissemination from advanced gastric cancer should be evaluated in future randomized clinical trials. Since the peritoneal dissemination from gastric cancer is considered to be an incurable disease, the patient's survival and quality of life will be important endpoints to be assessed in the future clinical trials. Recently, various new drugs with different mechanisms of action have been developed. However, since the patients whose main diseases are peritoneal dissemination are usually excluded from the phase II trials of new drugs or new combination regimens because of the lack of measurable lesions in those patients, the available data as to the efficacy against peritoneal dissemination are very limited unless we conduct trials specifically designed for this purpose as the present study. We think it is important to assess the roles of new drugs from the viewpoint of how we can maximize the potential value of each drug or regimen in disease-specific clinical situations. In this study we have focused on peritoneal dissemination with malignant ascites from advanced gastric cancer, which is very common and a major clinical problem. At present, any 5FU-based combination chemotherapies cannot prolong overall survival compared with 5FU alone. However, the present study brought us to the hypothesis that if we choose an appropriate regimen and administer it to the appropriate patient population (for example, to choose MTX/5FU therapy for the patients with peritoneal dissemination), survival may be prolonged compared with 5FU alone. We think that MTX/5FU therapy is the most reasonable regimen to be tested as a first-line chemotherapy in patients with peritoneal dissemination from advanced gastric cancer. From this clinical standpoint, a phase III randomized controlled trial comparing sequential MTX/5FU therapy with infusional 5FU-monotherapy (800 mg/m^2 of 5FU continuous infusion over 5 days every 4 weeks) in patients with advanced gastric cancer who have peritoneal dissemination with or without ascites is currently being carried out by the Japan Clinical Oncology Group (JCOG 0106-MF study). As a final note, we suggest that in future trials we should investigate the therapeutic strategy not only with newer cytotoxic drugs including irinotecan, taxanes and oxaliplatine, but also with new molecular targeting drugs such as antibody, VEGF drugs and EGF drugs, to bring about a breakthrough in this dire clinical condition.

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References

1. Glimelius B, Hoffman K, Haglund U. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994;5: 189–90.
2. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodriguez MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41.
3. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;71:587–91.
4. Dupont JB Jr, Lee JR, Burton GR, Cohn I Jr. Adenocarcinoma of the stomach: review of 1497 cases. *Cancer* 1987;41:941–7.
5. Brenner DE. Intraperitoneal chemotherapy: a review. *J Clin Oncol* 1986; 4:1135–47.

6. Nakajima T. Tabular analysis of 10 000 cases of gastric cancer. *Jpn J Cancer Chemother* 1994;21:1813–97.
7. Los G, Mutsaers PH, van der Vijgh WJ, Baldew GS, de Graaf PW, McVie JG. Direct diffusion of *cis*-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res* 1989;49:3380–4.
8. Rustum YM, Cao S, Zhang Z. Rationale for treatment design: Biochemical modulation of 5-fluorouracil by leucovorin. *Cancer J Sci Am* 1998;4: 12–8.
9. Labianca R, Pessi A, Facendola G, Pirovano M, Luporini G. Modulated 5-fluorouracil (5-FU) regimens in advanced colorectal cancer: a critical review of comparative studies. *Eur J Cancer* 1996 (Suppl 5);32A:S7–12.
10. Fernandes DJ, Bertino JR. 5-Fluorouracil-methotrexate synergy: enhancement of 5-fluorodeoxyuridylate binding to thymidylate synthase by dihydropteroylpolyglutamates. *Proc Natl Acad Sci USA* 1980;77:5663–7.
11. Cadman E, Heimer R, Davis L. Enhanced 5-fluorouracil nucleotide formation after methotrexate administration: explanation for drug synergism. *Science* 1979;205:1135–7.
12. Advanced Colorectal Cancer Meta-Analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994;12:960–9.
13. Perez JE, Lacava JA, Dominguez ME, Rodriguez R, Barbieri MR, Ortiz EH, et al. Biochemical modulation of 5-fluorouracil by methotrexate in patients with advanced gastric carcinoma. *Am J Clin Oncol* 1998;21:452–7.
14. Dickinson R, Preagrave P, Levi J, Milliken S, Woods R. Sequential moderate-dose methotrexate and 5-fluorouracil in advanced gastric adenocarcinoma. *Cancer Chemother Pharmacol* 1989;24:67–8.
15. Sasaki T, Ota K, Ibayashi J, Sakata Y, Matsuoka T, Ishikawa M, et al. Randomized multicenter trial of sequential methotrexate and 5-fluorouracil versus 5-fluorouracil alone in advanced gastric cancer. *Jpn J Cancer Chemother* 1989;16:2545–55 (in Japanese with English abstract).
16. Konishi T, Hiraishi M, Mafune K, Miyama T, Hirata T, Mori K, et al. Therapeutic efficacy and toxicity of sequential methotrexate and 5-fluorouracil in gastric cancer. *Anticancer Res* 1994;14:1277–80.
17. Japanese Research Society for Gastric Cancer. Response assessment of chemotherapy for gastric carcinoma. Japanese Classification of Gastric Carcinoma, 1st Engl ed. Tokyo: Kanehara 1995; 90–104.
18. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 1993;23:250–7.
19. Cullinan SA, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE, et al. Controlled evaluation of three drug combination regimens vs. fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. *J Clin Oncol* 1994;12:412–6.
20. Kim NK, Park YS, Heo DS, Suh G, Kim SY, Park KC, et al. A phase III randomized study of 5-fluorouracil and cisplatin vs. 5-fluorouracil, doxorubicin and mitomycin C vs. 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer* 1993;71:3813–8.
21. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG 9205). *J Clin Oncol* 2003;21:54–9.
22. Vanhoefer U, Rougier P, Wilke M, Ducreux MP, Lacave AJ, Van Cutsem E, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil and doxorubicin vs. etoposide, leucovorin and 5-fluorouracil vs. infusional 5-fluorouracil and cisplatin in advanced gastric cancer; a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000;18:2648–57.
23. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin and 5-fluorouracil vs. 5-fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261–7.
24. Ajani JA. Standard chemotherapy for gastric carcinoma: is it a myth? *J Clin Oncol* 2000;18:4001–3.
25. Dupont JB, Lee JR, Burton GR, Cohn I Jr. Adenocarcinoma of the stomach: review of 1,497 cases. *Cancer* 1978;41:941–7.
26. Dedric RL, Myers CE, Bungay PM, DeVita VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978;62:1–11.
27. Reichman B, Markman M, Hakes T, Kemeny N, Kelsen D, Hoskins W, et al. Phase I trial of concurrent intraperitoneal and continuous intravenous infusion of fluorouracil in patients with refractory cancer. *J Clin Oncol* 1988;6:158–62.
28. Markman M, Reichman B, Hakes T, Lewis JL Jr, Jones W, Rubin S, et al. Impact on survival of surgically defined favorable responses to salvage intraperitoneal chemotherapy in small-volume residual ovarian cancer. *J Clin Oncol* 1992;10:1479–84.
29. Chabner BA, Stoller RG, Hande K, Jacobs S, Young RC. Methotrexate disposition in humans: *Drug Metab Rev* 1978;8:107–17.
30. Konishi T, Miyama T, Sakamoto S, Hirata T, Mafune K, Hiraishi M, et al. Activity of thymidylate synthetase and thymidine kinase in gastric cancer. *Surg Oncol* 1992;1:215–21.