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Use of a combination of computed tomography and endoscopy to assess the response to 5-fluorouracil/cisplatin and predict survival in gastric cancer

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Background. Response of metastatic sites on computed tomography (CT) has been used to assess response in metastatic gastric carcinoma (MGC); however, the role of endoscopy to evaluate the response of the primary gastric lesion is unclear. We undertook a prospective study to compare prognostic values of endoscopy-based response criteria with those of CT-based response criteria in MGC patients treated with 5-fluorouracil (5-FU) and cisplatin. ***Methods.*** MGC patients naïve to chemotherapy were treated with 5-FU (1000 mg/m^2, days 1–5) and cisplatin (60 mg/m^2, day 1) (FP) every 21 days. Response was assessed by CT [World Health Organization (WHO) criteria/Response Evaluation Criteria In Solid Tumors (RECIST)] every three cycles and/or endoscopy after the third cycle. ***Results.*** With a median follow-up of 26.2 months, 103 patients were assessed by CT and endoscopy. There was good concordance between the WHO and RECIST criteria ($\kappa = 0.91$; $P = 0.0001$), but poor agreement between CT and endoscopic assessments ($\kappa = 0.17$; $P = 0.01$). On multivariate analysis, both CT (WHO/RECIST) (hazard ratio, 5.20; $P < 0.0001$) and endoscopic response (hazard ratio, 2.78; $P < 0.0001$) were significantly associated with survival. The combination of CT and endoscopy defined patients into four groups with distinct prognoses according to chemotherapy response: responders on both tests, responders on CT alone, responders on endoscopy alone, and nonresponders on both tests (hazard ratio, 1.00 versus 2.87 versus 5.35 versus 12.3; $P < 0.0001$). ***Conclusions.*** The use of endoscopy together with CT provides a better prognostic tool than CT alone in MGC patients treated with FP.

Key words: computed tomography, endoscopy, gastric cancer, 5-fluorouracil, cisplatin

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Introduction

Palliative chemotherapy is frequently used in patients with metastatic gastric carcinoma (MGC). Response to chemotherapy and survival are closely linked in chemotherapy of many solid tumors, including gastric cancer.[1,2] To accurately evaluate the effectiveness of chemotherapy in MGC, it is therefore important to determine the best method for evaluating response.

Tumor response to treatment has traditionally been assessed by measuring two dimensions of the tumor, the longest diameter and the diameter perpendicular to it, on radiographic images [the World Health Organization (WHO) criteria].[3] The newly introduced Response Evaluation Criteria In Solid Tumors (RECIST) uses a unidimensional measurement alone, the longest diameter, and was intended to further simplify the assessment of tumor response.[4] Although RECIST has been validated in a retrospective analysis of 14 large clinical trials involving more than 4000 patients, this analysis did not include patients with gastric cancer.[4] Recently, several types of solid tumor, including lung, breast, colon, and gastric cancer, were reassessed to validate RECIST; it was concluded that the unidimensional tumor measurements were equivalent to bidimensional criteria in assessing response rates.[5–9] The WHO and RECIST criteria define a clinical response as some measurable reduction in total tumor burden. Because neither WHO nor RECIST considers gastric tumor lesions as "measurable," primary gastric lesions cannot be assessed by these criteria. In 1985, the Japanese Research Society for Gastric Cancer established assessment criteria for gastric cancer, including quantitative measurements of primary tumor response. These criteria, which were further refined in 1999,[10,11] use X-ray and endoscopic findings to assess primary gastric lesions. The prognostic value of these endoscopy-based response criteria, however, has not been fully evaluated yet. Therefore, we undertook a prospective study to compare

prognostic values of endoscopy-based response criteria with those of computed tomography (CT)-based response criteria (WHO and RECIST) in MGC patients treated with 5-FU and cisplatin.

Patients and methods

Patients

To be eligible for this trial, patients were required to be aged 18 years and above; to have histologically proven MGC; at least one clinically or radiographically measurable lesion; an endoscopically determined gastric tumor lesion, except for Borrmann type IV lesions; no prior chemotherapy; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–3. In addition, patients had to have adequate baseline hematological function [white blood cell (WBC) count ≥4000/mm^3 and platelet count ≥100 000/mm^3], hepatic function (serum aspartate aminotransferase and alanine aminotransferase ≤2.0 × the upper normal limit and serum bilirubin <2.0 mg/dl), and renal function (serum creatinine <1.5 mg/dl or creatinine clearance >50 ml/min).

Patients excluded from this trial were those with a history of other malignancies within the previous 5 years, except for basal cell carcinoma of the skin or adequately treated carcinoma in situ of the cervix; preexisting peripheral neuropathy of grade ≥2 of any origin; uncontrolled concurrent medical illness; active angina or myocardial infarction; or congestive heart failure within the previous 6 months. This study was approved by the institutional review board. All patients gave written informed consent before participation in the study.

Treatments

5-Fluorouracil (5-FU) (1000 mg/m^2) was administered as a 12-h intravenous (i.v.) infusion on days 1–5 and cisplatin (60 mg/m^2) as a 15-min i.v. infusion on day 1. The cycle was repeated every 21 days. Treatment was continued until disease progression or unacceptable toxicity developed.

Dose modifications

Toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 was evaluated before each treatment cycle. The next chemotherapy cycle was started if the WBC count on the day of treatment was ≥3000/mm^3 and if nonhematological toxicity resolved or improved to grade 1 or 0.

In patients experiencing grade 3 or 4 neutropenia with fever or any grade ≥3 nonhematological toxicity except nausea/vomiting, the dose of 5-FU was reduced by 25% in subsequent cycles. In patients with grade 2 or 3 neurological toxicity or grade ≥3 nonhematological toxicity, the dose of cisplatin was reduced by 25% in subsequent cycles. Dose escalation after dose reduction was not permitted. Patients with poor PS (ECOG ≥ 2) were started with 3 days of 5-FU combined with cisplatin. Elderly (>70 years) patients could be treated with 25% reductions in the dose of 5-FU and/or cisplatin.

Assessment of response

Pretreatment evaluation included a determination of medical history, physical examination, complete blood cell count with differential, platelet count, blood chemistry, endoscopy, and CT scan of the abdomen performed within 1 month before treatment. A CT scan was performed every three cycles unless more frequent scans were clinically indicated. Patients were considered assessable for response if they had at least one follow-up assessment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to the WHO and RECIST criteria (Table 1).

Endoscopic assessment of treatment response was done after three cycles of chemotherapy, based on Japanese Gastric Cancer Association criteria (Table 2).[10,11] Because confirmatory endoscopy was not mandatory

Table 1. Definition of tumor response according to the WHO and RECIST criteria

	WHO	RECIST
Measurability	Measurable, bidimensional	Measurable, unidimensional
Objective response:		
Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 50% decrease; confirmed at 4 weeks	At least 30% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met
Progressive disease (PD)	25% increase; no CR, PR, or SD documented before increased disease, or new lesion(s)	20% increase; no CR, PR, or SD documented before increased disease, or new lesion(s)

WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors

Table 2. Definition of primary gastric tumor lesion response according to Japanese criteria

	Measurable lesion	Not measurable, but evaluable lesion
Objective response:		
Complete response (CR)	Disappearance of all known lesion(s); confirmed pathologically with repeat primary site biopsy	Disappearance of all known lesion(s); confirmed pathologically with repeat primary site biopsy
Partial response (PR)	At least 50% decrease in the product of the longest diameter and the longest rectangular diameter of total tumor size in two-dimensional measurable lesions; at least 30% decrease in total tumor size in one-dimensional measurable lesions	Dramatic regression such as flattening on endoscopic examination, which roughly corresponds to at least a 50% decrease in tumor size
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met
Progressive disease (PD)	Exacerbation of tumor size or endoscopic findings (at least a 25% increase in measurable lesions) or the appearance of new lesions	Exacerbation of tumor size or endoscopic findings or the sappearance of new lesions

according to these criteria, further endoscopy was not routinely done thereafter, unless either the patient's symptoms or CT suggest disease progression. Response according to the combined method was categorized by combining the results of endoscopy (response versus nonresponse) and CT (response versus nonresponse) for each patient.

Statistical analysis

The kappa coefficient of reliability was used to test the concordance of the tumor response as determined by CT scans (WHO versus RECIST criteria) and endoscopic data.

Overall survival was defined as the time from the initiation of treatment to the date of death. Survival probability analyses were performed using the Kaplan–Meier method. Univariate survival analysis was carried out by means of log-rank test; multivariate analysis was performed with the Cox's proportional hazard model.

Results

Patient characteristics

From June 2001 to October 2004, 103 patients were enrolled in this study, 77 (74.8%) men and 26 (25.2%) women, of median age 57 years (range, 21–76 years). Most of the patients (93.2%) had ECOG PS 0-1, and 74 (71.8%) had multiple metastases involving two or more organ systems. Metastatic organ sites were in the distant abdominal lymph nodes ($n = 60$, 58.3%), peritoneum ($n = 56$, 54.4%), liver ($n = 64$, 62.1%), and others ($n = 34$, 33.0%) (Table 3).

Treatment delivered

A total of 588 cycles were administered to these 103 patients, with a median of 5 cycles per patient (range, 1–19 cycles). Treatment was stopped because of disease progression in 99 patients (96.1%) and sepsis in 1 patient (1.0%); the remaining 3 patients (2.9%) were lost to follow-up.

Evaluation of tumor response using CT and endoscopy

All 103 patients treated with 5-FU and cisplatin were evaluated for response by both CT and endoscopy, with the former assessed by both WHO and RECIST criteria. When we compared results according to the WHO and RECIST criteria (Table 4), we observed concordant findings in 97 of the 103 patients (94.2%) ($\kappa = 0.91$; $P = 0.0001$). In the remaining 6 patients (5.8%), the results were discordant. One patient with PR based on the WHO criteria had SD according to RECIST criteria; 2 patients with SD according to the WHO criteria were classified as PR and PD, respectively, by RECIST criteria; and 3 patients with PD based on the WHO criteria were classified as SD according to RECIST criteria. Thus, compared with the WHO criteria, the RECIST criteria showed a better response in 4 patients and a poorer response in 2 patients. The overall response rate was identical in 31/103 patients (30.1%).

When we compared endoscopy-based and CT-based responses in this patient cohort (see Table 4), we found that they were not completely consistent with each other, with a κ coefficient of reliability of 0.17 ($P = 0.01$).

Table 3. Patient characteristics ($n = 103$)

Characteristic	Number (%)
Median age (years) (range)	57 (21–76)
Sex	
Male	77 (74.8)
Female	26 (25.2)
ECOG performance status	
0	16 (15.5)
1	80 (77.7)
2	6 (5.8)
3	1 (1.0)
Histology	
Adenocarcinoma, tubular, well differentiated	1 (1.0)
Adenocarcinoma, tubular, moderately differentiated	37 (35.9)
Adenocarcinoma, tubular, poorly differentiated	53 (51.5)
Signet ring cell carcinoma	12 (11.6)
Metastatic organ sites	
Distant abdominal lymph node	60 (58.3)
Peritoneum	56 (54.4)
Liver	64 (62.1)
Others[a]	34 (33.0)
Number of metastatic organ sites	
1	29 (28.2)
2	44 (42.7)
≥3	30 (29.1)

ECOG, Eastern Cooperative Oncology Group
[a] Lung, cervical lymph node, ovary, bone, adrenal gland, kidney, chest wall, skin, bladder

Table 4. Response assessment according to computed tomography (CT)-based criteria (WHO and RECIST) and endoscopy-based criteria ($n = 103$)

Endoscopy response	CT response according to WHO (RECIST) criteria				
	CR	PR	SD	PD	Total
CR	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
PR	0 (0)	15 (14)	13 (14)	3 (3)	31 (31)
SD	0 (0)	14 (15)	26 (26)	16 (15)	56 (56)
PD	0 (0)	1 (1)	4 (5)	10 (9)	15 (15)
Total	0 (0)	31 (31)	43 (45)	29 (27)	103

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

Univariate survival analysis

At the time of analysis, 79 of the 103 patients were known to have died. Estimated median follow-up duration was 26.2 months (range, 3.6–42.0 months). The estimated median overall survival was 8.7 months [95% confidence interval (CI), 6.9–10.5 months].

Both the CT (WHO and RECIST criteria) and endoscopy assessments of response were significantly associated with overall survival duration (CT, $P < 0.0001$; endoscopy, $P = 0.0006$). With the CT assessment, the median survival of responders (CR and PR) was 21.1 months (95% CI, 13.1–29.1 months) and the median survival of nonresponders (SD and PD) was 7.6 months (95% CI, 6.8–8.4 months). With the endoscopy assessment, the median survival of responders and nonresponders was 18.8 months (95% CI, 15.3–22.3 months) and 7.9 months (95% CI, 7.0–8.8 months), respectively. Using a combination of CT and endoscopy responses, we observed a significant correlation between response and survival ($P < 0.0001$) (Table 5, Fig. 1). However, the survival curves of each response category differed according to the method used (Fig. 1). Using the combination of CT and endoscopy, the response classification defined groups with distinct prognoses. The median survival and 1-year survival rates of patients with response based on both CT (RECIST) and endoscopy were 26.7 months (95% CI, 20.3–33.1 months) and 92.9% ± 6.9%, respectively. The median survival and 1-year survival rates of patients with re-

Table 5. Association of CT (WHO and RECIST criteria) and endoscopic response with survival duration

Response	Number	Median survival (months)	95% CI	1-year survival rate (%)	*P* value
CT response (WHO)					
Response	31	23.5	15.7–31.3	82.3 ± 7.2	<0.0001
Nonresponse	72	7.6	6.8–8.4	20.0 ± 5.1	
CT response (RECIST)					
Response	31	21.1	13.1–29.1	78.2 ± 7.9	<0.0001
Nonresponse	72	7.6	6.8–8.4	21.8 ± 5.2	
Endoscopic response					
Response	32	18.8	15.3–22.3	65.5 ± 8.9	0.0001
Nonresponse	71	7.9	7.0–8.8	26.4 ± 5.6	
Response according to RECIST and endoscopy					
Response per both RECIST and endoscopy	15	26.7	20.3–33.1	92.9 ± 6.9	<0.0001
Response per RECIST only	16	15.4	8.6–22.2	63.6 ± 13.3	
Response per endoscopy only	17	9.3	3.5–15.1	39.7 ± 13.0	
No response per both RECIST and endoscopy	55	7.3	6.5–8.1	16.1 ± 5.3	

CI, confidence interval

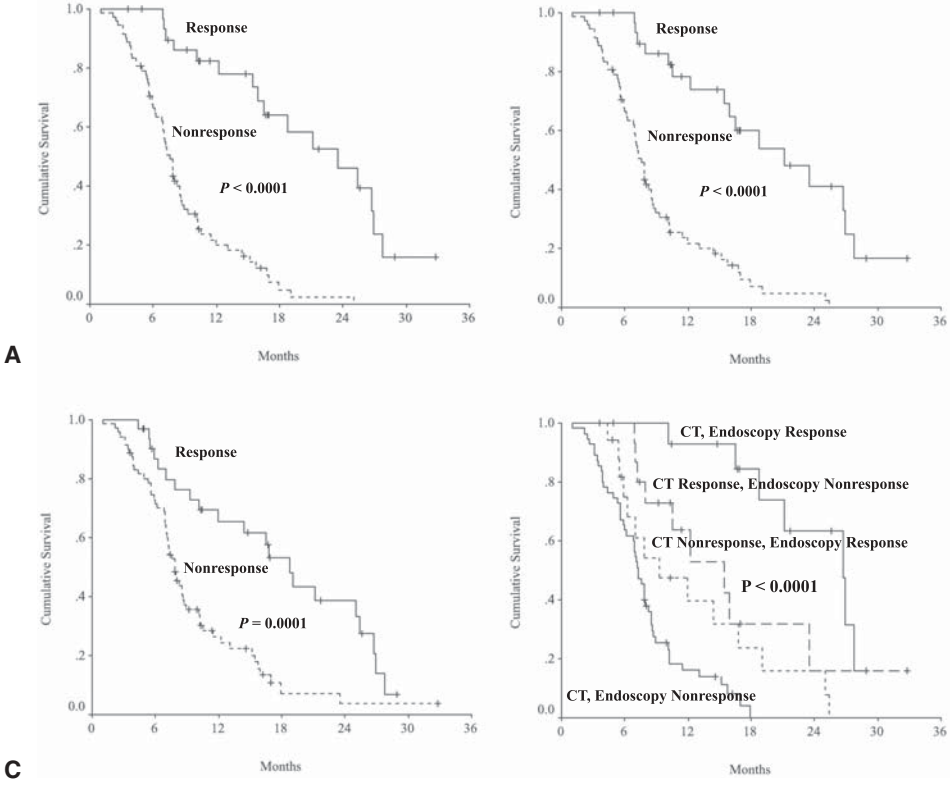

Fig. 1A–D. Effect of computed tomography (CT) and endoscopic response on survival. A Cumulative survival according to CT response per World Health Organization (WHO) criteria. B Cumulative survival according to CT response per Response Evaluation Criteria in Solid Tumors (RECIST). C Cumulative survival according to endoscopic response. D Cumulative survival according to combined CT (RECIST) and endoscopy responses

sponse based on CT and nonresponse on endoscopy were 15.4 months (95% CI, 8.6–22.2 months) and 63.6% ± 13.3%, respectively. In the patients with nonresponse based on CT and response based on endoscopy, the median survival and 1-year survival rates were 9.3 months (95% CI, 3.5–15.1 months) and 39.7% ± 13.0%, whereas in the patients with nonresponse based on both tests, the median survival and 1-year survival rates were 7.3 months (95% CI, 6.5–8.1 months) and 16.1% ± 5.3% ($P < 0.0001$), respectively. Using the WHO criteria in place of RECIST, similar results were observed (data not shown).

Table 6. Multivariate analyses

Factors	HR (95% CI)
Analysis 1[a]	
RECIST-defined response alone	
Response	1.00
Nonresponse	5.20 (2.68–10.1)
ECOG performance status	
0–1	1.00
2–3	2.56 (1.09–6.02)
Histology	
Well/moderately differentiated ADC	1.00
Poorly differentiated ADC/SRC	2.06 (1.20–3.53)
Analysis 2[a]	
Endoscopy-based response alone	
Response	1.00
Nonresponse	2.78 (1.60–4.80)
ECOG performance status	
0–1	1.00
2–3	4.01 (1.70–9.48)
Histology	
Well/moderately differentiated ADC	1.00
Poorly differentiated ADC/SRC	2.09 (1.22–3.58)
Analysis 3[a]	
Response according to RECIST and endoscopy	
Response per both RECIST and endoscopy	1.00
Response per RECIST only	2.87 (1.10–8.12)
Response per endoscopy only	5.35 (1.87–15.2)
No response per both RECIST and endoscopy	12.3 (4.60–32.7)
ECOG performance status	
0–1	1.00
2–3	2.75 (1.16–6.54)
Histology	
Well/moderately differentiated ADC	1.00
Poorly differentiated ADC/SRC	2.19 (1.27–3.77)

HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SRC, signet ring cell carcinoma
[a] No independent prognostic value was found for any of the following covariate: age, sex, number of metastatic organ sites

Patient median survival was also significantly different according to ECOG PS (10.1 months for patient with ECOG PS 0/1 versus 4.0 months for patients with ECOG PS 2/3; $P = 0.0001$) and histology (12.2 months for patients with well/moderately differentiated adenocarcinoma versus 8.0 months for patients with poorly differentiated adenocarcinoma/signet ring cell carcinoma; $P = 0.003$).

Multivariate analysis

The results from the multivariate Cox analyses are shown in Table 6. ECOG PS, age at diagnosis, sex, histology, number of metastatic sites, and treatment response were entered into the model, with treatment response calculated by CT response according to RECIST, endoscopic response, and the combined response of CT and endoscopy. Even after adjusted for PS and histology, endoscopy-based treatment response and RECIST, either alone (analyses 1 and 2) or in combination (analysis 3), turned out to be independent prognostic factors. Similar findings were observed when the WHO criteria were substituted for RECIST in these models (data not shown).

Discussion

The recently introduced RECIST using unidimensional measurements provide a simpler method than the WHO criteria, which use bidimensional measurements. Moreover, the RECIST have been validated in several studies, showing concordance of overall response with the WHO criteria.[4–9] In patients with MGC, however, there have been no reports correlating treatment response according to RECIST and patient survival.

In this study, we prospectively compared the two techniques for assessment of tumor response in MGC patients treated with 5-FU plus cisplatin. There was excellent agreement between the results obtained using the unidimensional and bidimensional criteria, with a concordance rate of 0.94 ($\kappa = 0.91$; $P = 0.0001$). Although the RECIST resulted in the reclassification of six patients (5.8%), the overall response rate of 30.1% was equivalent according to both WHO and RECIST criteria. Our study thus provides evidence for the accuracy and usefulness of RECIST and validates its use in patients with gastric cancer.

CT-based response criteria, either RECIST or WHO, entail the direct measurements of lesions as the indicator of response. On CT, however, primary gastric tumor lesions that appear as a thickened gastric wall are not considered measurable lesions and are therefore not included in the overall evaluation of tumor response according to WHO or RECIST criteria. The prognostic significance of response at the primary site of gastric tumors is not clear. In addition, many patients with MGC have small measurable lesions or nonmeasurable lesions on CT, including small peritoneal nodules or peritoneal wall thickening in patients with peritoneal seeding. For such patients, CT-based methods may be less informative than endoscopy-based assessment. The response of primary gastric lesions to chemotherapy with tegafur or UFT combined with mitomycin C has been associated with improved survival in patients with unresectable advanced gastric cancer, regardless of the response of metastatic lesions.[2]

Moreover, in a retrospective study, patients with primary gastric lesions who responded to treatment, as assessed by Japanese criteria, had superior survival compared with nonresponders than patients with metastatic lesions who were responders according to WHO criteria.[12] These findings, however, were not validated using multivariate analysis containing other potential prognostic variables. In contrast, our study provides multivariate analysis data for the prognostic value of endoscopy-based response assessment combined with conventional CT-based criteria. This study demonstrates that response assessment by a combination of CT and endoscopy is superior to CT alone, using either WHO or RECIST criteria, or endoscopy alone in predicting survival in this group of patients. In the multivariate analysis containing potential prognostic factors (age, sex, PS, histology, and number of metastatic sites), the endoscopy-based response and RECIST were found to be independent prognostic factors for survival, either alone or in combination. The addition of endoscopic assessment to CT predicted the response-survival relationship better than did CT or endoscopy alone, and provided a subdivision of patients with or without response in CT into groups having different prognoses; among CT-defined responders, endoscopy-defined responders had significantly prolonged duration of survival compared to endoscopy-defined nonresponders (26.7 versus 15.4 months). Similarly, among CT-defined nonresponders, endoscopy-defined nonresponders had significantly shortened duration of survival compared to endoscopy-defined responders (7.3 versus 9.3 months) (see Table 5, Fig. 1D). Evidently, however, the response assessment based on endoscopy alone had inferior prognostic value to CT-based methods. In this regard, the improved prognostic value achieved by the addition of endoscopy to conventional CT-based response assessment should be weighed carefully against the risk and cost involving endoscopy procedure (of each health care system).

We also found a poor agreement between the CT and endoscopic assessments, with a kappa value of 0.17 ($P = 0.01$) (see Table 4). Using the RECIST, the assessments were equal in only 49 patients (47.6%) in two tests. A major discrepancy was defined as the conclusion of PR using one method and of SD using the other. Our study is limited by the fact that endoscopic response was assessed after three cycles of chemotherapy. In contrast, CT-based response was determined as the best response of all assessments done every three cycles, according to RECIST or WHO criteria. This fact could be partly responsible for the discrepancy between CT-based and endoscopy-based responses.

In conclusion, multivariate analysis showed that an endoscopically determined response to palliative 5-FU and cisplatin is associated with improved survival in patients with MGC. The combination of endoscopic and CT results, whether using WHO or RECIST criteria, led to the best response–survival relationship, with more sophisticated classification of patients into four groups having different survival rates. This combined method of response assessment was validated in the multivariate Cox analysis. We also found that unidimensional tumor measurement by CT (RECIST) was as effective as bidimensional measurement (WHO criteria) for categorizing overall tumor response and predicting survival in MGC.

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