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ORIGINAL ARTICLE

Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients

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Abstract
Background The Response Evaluation Criteria in Solid Tumors (RECIST) was revised in 2009, based on a large dataset of 6512 patients from 16 trials. However, no gastric cancer patients were included in those data. The purpose of this study was to clarify the difference between RECIST version 1.0 and version 1.1 in advanced gastric cancer.
Methods From 2004 to 2009, 129 consecutive patients with advanced gastric cancer received S-1 plus cisplatin as first-line treatment at the National Cancer Center Hospital East. Ninety-seven of these patients who had had baseline and post-treatment computed tomography scans performed were included in this study. Measurements of tumors were conducted retrospectively.
Results At the baseline of first-line chemotherapy, 172 lymph nodes in 54 patients were considered to be candidate target lesions by RECIST version 1.0. However, only 38 % of the lymph nodes were classified as target lesions by RECIST version 1.1, with 47 % classified as non-target lesions and 15 % classified as non-pathological. By RECIST version 1.0, the proportion of patients with target lesions at the baseline of first-line chemotherapy was 67 % (65/97), and this percentage was significantly reduced according to RECIST version 1.1 (53 %; 51/97) (McNemar's exact test, $P < 0.001$). The findings at the baseline of second-line chemotherapy were similar (reduced from 62 to 49 %; McNemar's exact test, $P = 0.002$). Overall response rates of first-line chemotherapy were 52 % (34/65) according to RECIST version 1.0 and 55 % (28/51) according to version 1.1.
Conclusions The revision of RECIST significantly reduced the proportion of patients classified with target lesions at the baselines of first-line and second-line chemotherapies. No obvious difference in overall response rates was observed.

Keywords RECIST · Gastric cancer · Target lesion

Introduction

The Response Evaluation Criteria in Solid Tumors (RECIST) have been widely used as standard criteria to evaluate the objective responses of chemotherapy, and the RECIST version 1.0 were revised to version 1.1 in 2009 [1, 2]. Major changes in the revised RECIST version 1.1 are as follows. (1) The number of lesions required to assess tumor burden has been reduced from a maximum of 10 to 5 in total, and from a maximum of 5 to 2 per organ. (2) Lymph nodes with a ≥15 mm short axis are considered measurable as target lesions, those with a ≥10 to <15 mm short axis are considered assessable as non-target lesions, and those with a <10 mm short axis are considered non-pathological. (3) Additionally, the definitions of complete response (CR) and progressive disease (PD) were revised. In the response criteria for CR, especially in regard to lymph node evaluation, the requirement for the disappearance of all lesions was revised to any pathological lymph nodes having a reduction in the short axis of <10 mm. In the response criteria for PD,

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RECIST version 1.1 requires a 5 mm absolute increase, in addition to a target lesion with a 20 % increase in the sum of the diameters, to avoid a clinically inappropriate diagnosis of PD when the total sum of lesion diameters is very small [1].

The revision, RECIST 1.1, was based on a large dataset (RECIST data warehouse) of 6512 patients from 16 clinical trials, consisting of 7 breast cancer trials, 4 lung cancer trials, 2 colorectal cancer trials, 2 renal cell carcinoma trials, and 1 gastrointestinal stromal tumor trial, performed between 1993 and 2005 [1, 2]. However, no gastric cancer patients were included in those data.

While surgery remains the only possible cure in patients with early-stage gastric cancer, palliative chemotherapy is the mainstay for patients with inoperable advanced or recurrent cancer. Although there is no globally accepted standard chemotherapy regimen, a fluoropyrimidine plus a platinum agent with or without epirubicin or docetaxel are the protocols used for advanced gastric cancer patients [3]. Based on several randomized controlled trials, a combination of tegafur, gimeracil, and potassium oxonate (S-1) plus cisplatin (CDDP) is widely used and accepted as standard chemotherapy in Japan [4–6].

The purpose of this study was to clarify the differences between RECIST version 1.0 and version 1.1 in terms of the proportions of patients classified with target lesions at the baselines of first- and second-line chemotherapies and the overall response rate (ORR) in advanced gastric cancer patients who received S-1 plus CDDP as first-line chemotherapy.

Patients and methods

From 2004 to 2009, 129 consecutive patients with advanced gastric cancer received S-1 plus CDDP as first-line treatment at the National Cancer Center Hospital East. S-1 (40–60 mg depending on the patient's body surface area as follows: <1.25 m^2, 40 mg; ≥ 1.25 m^2 and <1.5 m^2, 50 mg; and ≥ 1.5 m^2, 60 mg) was given orally twice daily for 3 consecutive weeks and CDDP was given intravenously at a dose of 60 mg/m^2 on day 8, followed by a 2-week rest period, within a 5-week cycle. Of all 129 patients, 97 patients who met the following criteria were included in this study: histologically confirmed unresectable and recurrent adenocarcinoma of the stomach, having no other malignancy, no history of chemotherapy or radiation therapy except for adjuvant chemotherapy, and tumor assessment by computed tomography (CT) scans performed in our hospital at baseline (within 28 days before the start of treatment) and post-treatment.

All CT scans were performed on a helical CT scanner with intravenous administration of contrast materials, and the slice thickness was 5 mm. The post-treatment CT scans were performed after every 2 cycles of S-1 plus CDDP. The CT image data were directly displayed on monitors and tumor measurements were performed with electronic calipers. We reviewed each patient's medical records and measured tumor size retrospectively using RECIST version 1.0 and version 1.1. Two medical oncologists (N.F. and E.N.) reviewed all CT images independently of the attending physicians. First, E.N. evaluated all CT images based on RECIST versions 1.0 and 1.1. N.F. then reviewed the results. If an inter-observer difference was present, the final judgment was made after sufficient discussion. The overall response was evaluated without interval confirmation.

The differences in proportions of patients with target lesions between the two RECIST versions were evaluated using McNemar's exact test. Corresponding 95 % confidence intervals (CIs) were also calculated, using the Clopper-Pearson method. All P values are two sided. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

All data were collected retrospectively. The study was performed under an institutional review board waiver in accordance with the Japanese ethical guidelines for epidemiological research.

Results

The characteristics of the 97 patients are shown in Table 1. All 97 patients discontinued S-1 plus CDDP, for the following reasons: 88 patients because of PD, 5 because of adverse events, and 4 for other reasons. Of the 88 patients with PD after S-1 plus CDDP, 74 (84 %) received second-line chemotherapy.

One hundred seventy-two lymph nodes from 54 patients were considered to be candidate target lesions by RECIST version 1.0 at the baseline of the first-line chemotherapy. These lymph nodes were categorized into 3 groups according to the size of the short axis by RECIST version 1.1 as follows: <10 mm; ≥ 10 mm but <15 mm; and ≥ 15 mm (Table 2). According to RECIST version 1.1, only 38 % (66/172) of the lymph nodes were classified as target lesions, 47 % (80/172) were classified as non-target lesions and 15 % (26/172) were classified as non-pathological lesions.

Target lesions at the baselines of the first- and second-line chemotherapies, classified according to RECIST version 1.0 and version 1.1, are summarized in Table 3. The proportion of patients with a target lesion at the baseline of the first-line chemotherapy was 67 % (65/97; 95 % CI 57–76 %) by RECIST version 1.0, and the proportion was reduced to 53 % (51/97; 95 % CI 42–63 %) when classified according to RECIST version 1.1. This reduction was statistically significant (McNemar's exact test, $P < 0.001$).

Table 1 Characteristics of the 97 patients

Characteristic	No. of patients	%
Median age, years (range)	64 (32–79)	
Gender		
Male	64	66
Female	33	34
Performance status		
0	65	67
1	31	32
2	1	1
Histology		
Undifferentiated	57	59
Differentiated	37	38
Not specified	3	3
Prior adjuvant chemotherapy		
Yes	5	5
No	92	95
Disease status		
Unresectable	83	86
Recurrent	14	14
Primary tumor		
Present	73	75
Absent	24	25
No. of organs involved		
1	38	39
2	44	45
≥3	15	16
Metastatic sites		
Lymph node	69	71
Peritoneal	60	62
Liver	31	32
Lung	2	2
Bone	6	6
Other	3	3

Table 2 Categorization of 172 lymph nodes that were candidate target lesions according to RECIST version 1.0

Classification	No. of lymph nodes	%
Non-pathological (short axis <10 mm)	26	15
Non-target (short axis ≥10, <15 mm)	80	47
Target (short axis ≥15 mm)	66	38

RECIST Response Evaluation Criteria in Solid Tumors

Of the 32 patients who did not have any target lesions at the baseline of the first-line chemotherapy, 21 had only peritoneal metastasis, 9 had peritoneal metastasis and lymph node metastasis, 1 had lymph node metastasis only, and 1 had peritoneal, lymph node, and bone metastases.

Table 3 Target lesions at the baselines of first- and second-line chemotherapies

	RECIST version 1.0		RECIST version 1.1	
	No. of patients	%	No. of patients	%
First-line ($n = 97$)				
Target lesion (+)	65	67	51	53
Target lesion (−)	32	33	46	47
Second-line ($n = 74$)				
Target lesion (+)	46	62	36	49
Target lesion (−)	28	38	38	51

RECIST Response Evaluation Criteria in Solid Tumors

Table 4 Overall response

	RECIST version 1.0 ($n = 65$)		RECIST version 1.1 ($n = 51$)	
	No. of patients	%	No. of patients	%
Overall response	34	52	28	55
Complete response	0	0	1	2
Partial response	34	52	27	53
Stable disease	26	40	19	37
Progressive disease	5	8	4	8

RECIST Response Evaluation Criteria in Solid Tumors

Of the 65 patients who had target lesions based on RECIST version 1.0 at the baseline of the first-line chemotherapy, 29 had only lymph node metastasis as a target lesion and 14 no longer had target lesions according to the RECIST revision. Of the 14 patients who no longer had target lesions after the RECIST revision, 5 patients had only lymph node metastasis; 7 had peritoneal metastasis (which was not considered as a target lesion), with lymph node metastasis; and 2 had bone metastasis with lymph node metastasis.

The proportion of patients with a target lesion at the baseline of the second-line chemotherapy was 62 % (46/74; 95 % CI 50–73 %) as classified by RECIST version 1.0, and this proportion was reduced to 49 % (36/74; 95 % CI 37–61 %) by RECIST version 1.1. The difference between the two RECIST versions in the proportions of patients with target lesions was statistically significant (McNemar's exact test, $P = 0.002$).

Overall response rates (ORRs), and the numbers of patients with CR, partial response (PR), stable disease, and PD after first-line chemotherapy are shown in Table 4. The ORRs of S-1 plus CDDP were 52 % (34/65) according to RECIST version 1.0 and 55 % (28/51) according to version 1.1. In 1 patient, while the overall response classified by

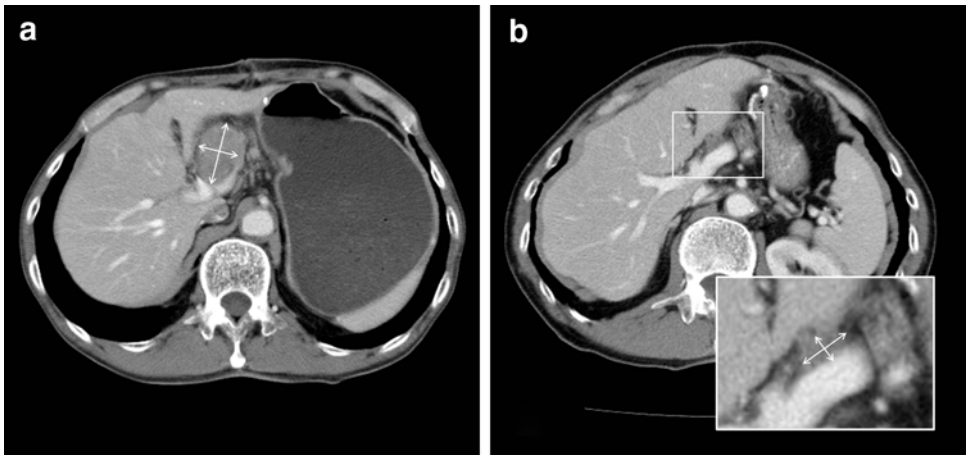

Fig. 1 Discrepancy between Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and RECIST version 1.1 in the overall response in 1 patient. A partial response classified by RECIST version 1.0 was changed to a complete response by RECIST version 1.1. **a** Lymph node metastasis, as the only target lesion, was 40 mm versus 27 mm (long axis vs. short axis) at the baseline of the first-line chemotherapy. **b** The lymph node had regressed to 14 versus 7 mm 1 year after the initiation of the first-line chemotherapy

RECIST version 1.0 was PR, the overall response classified by RECIST version 1.1 was CR (Fig. 1).

Discussion

Our data showed that the revision of RECIST significantly decreased the proportions of patients classified with target lesions at the baselines of both the first-line and second-line chemotherapies. The decrease in the numbers of patients classified with target lesions in RECIST version 1.1 was caused by the change in lymph node evaluation. From the RECIST data warehouse, 90.5 % of lymph nodes were considered to be target lesions according to the new guidelines of RECIST version 1.1 [7]. In contrast, in our study, only 38 % of lymph nodes were considered to be target lesions based on RECIST version 1.1. This large difference between studies might be caused by the characteristics of lymph node metastasis from gastric cancer being different from those of the lymph nodes in the RECIST data warehouse. However, the evaluation of lymph nodes in the RECIST data warehouse was based on only 2747 bidimensionally measurable lesions from all 3974 lesions [7]. This selection might have been biased and it might explain the discordance between the RECIST data warehouse results and our study.

A decrease in the number of patients with target lesions may affect the eligibility of patients for a clinical trial, because some trials, particularly phase II studies or phase III studies in which progression-free survival is a primary endpoint, require a target lesion in the eligibility criteria. The proportions of patients with target lesions in clinical trials that do not require a target lesion in the eligibility criteria differ between trials and regions. While the proportion of patients with target lesions was relatively small in recent Japanese trials (59–76 %) [5, 6, 8, 9], the proportion was 96 % in the FLAGS study, which was conducted in the rest of the world [10]. In the AVAGAST study, 73 % of Asian patients had target lesions, while 88 % of European and 77 % of Pan-American patients had target lesions [11]. In the Japan Clinical Oncology Group (JCOG) 9912 study, patients without target lesions had better survivals than those with target lesions [12]. The fact that more patients without target lesions participated in clinical trials in Japanese and other Asian studies might explain why there was a better prognosis in Japanese or Asian patients. This hypothesis needs to be evaluated by data from global clinical trials.

We found that the ORRs of S-1 plus CDDP were similar in RECIST version 1.0 and version 1.1 (52 and 55 %, respectively). In our study, the overall response was determined without interval confirmation, because of the limitation of it being a retrospective study. CT scans were performed after every 2 cycles of S-1 plus CDDP in a practice setting, which was translated into an interval of $\geq$10 weeks, while CT scans are performed at an interval of 4–6 weeks in clinical trials in which the primary endpoint is the ORR. The number of patients classified as responders would increase without response confirmation [2]. Accurate evaluation of differences in the ORRs between RECIST version 1.0 and version 1.1 will require data of clinical trials in which CT scans are performed at a short-term interval.

In conclusion, for advanced gastric cancer patients, the revision of RECIST significantly reduced the proportions of patients classified with target lesions at the baselines of

first-line and second-line chemotherapies. There did not appear to be a difference between the two RECIST versions in the response rates of first-line chemotherapy.

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Conflict of interest None of the authors has financial or personal conflicts of interest to disclose.

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