Diagnostic validity of CT gastrography versus gastroscopy for primary lesions in gastric cancer: evaluating the response to chemotherapy, a retrospective analysis

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Received: 6 June 2012 / Accepted: 2 November 2012 / Published online: 29 November 2012
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Abstract

Background This retrospective study was carried out to compare computed tomographic (CT) gastrography and conventional optical gastroscopy (GS) in order to evaluate the effectiveness of chemotherapy in primary gastric lesions.

Methods Patients with unresectable advanced and unresected early gastric cancer who had primary lesions and had received chemotherapy were enrolled. For primary lesions, CT gastrography and endoscopic assessment were done after chemotherapy, based on the Japanese Classification of Gastric Carcinoma (JCGC) criteria, 13th edition, and the Response Evaluation Criteria in Solid Tumors (RECIST). For metastatic solid lesions including lymph nodes, CT assessment was done based on the RECIST criteria.

Results Data from 23 patients were analyzed. With median follow-up of 9.4 months (range 2–23 months), 58 examinations were assessed by GS and CT gastrography.

Setting optical endoscopic results as the gold standard, the accuracy of CT gastrography for primary gastric lesions was 77.6 % (45 of 58) (weighted $\kappa = 0.72$; $P < 0.01$) according to the JCGC 13th edition criteria and 90.0 % (52 of 58) (weighted $\kappa = 0.75$; $P < 0.01$) according to the RECIST. When all results were divided into two groups [the non-progressive disease (non-PD) group and PD group], accuracy was 93.1 % (52 of 58) ($\kappa = 0.81$; $P < 0.01$), sensitivity was 100 %, and specificity was 75.0 % (12 of 16). In addition, the predictability of PD was 100 % (12 of 12). The four cases of failure in specification were the following: a case of gastric remnant cancer, a case with insufficient distension of the stomach, a healed case with stenosis and scarring, and a case in which the wrong position had been selected for the examination. The average period until PD was 9.9 months (range 5–18 months), and the concordance period between GS and CT gastrography was 7.2 months in both non-PD and PD cases.

Conclusions There was good concordance between the evaluations of GS and CT gastrography. CT gastrography exhibited favorable results in accuracy as well as 100 % PD predictability, which implied the possibility of using CT gastrography as a substitute for endoscopic assessments at post-chemotherapy assessments.

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Keywords Gastric cancer · CT gastrography ·
Chemotherapy · Primary lesion · JCGC

Introduction

The Guidelines of the Japanese Classification of Gastric Carcinoma (JCGC), 14th edition [1], adopted the usage of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [2] as the post-chemotherapy assessment;

however, the primary lesion of gastric cancer was defined as a non-target lesion because of the difficulties conducting objective assessments. However, it has also been reported [3, 4] that the response at the primary gastric cancer lesion better predicts the precise convalescence. As the 14th edition of the JCGC treated the assessment results of the primary lesion as only a reference opinion, patients need to undergo gastroscopy (GS) and upper gastrointestinal X-ray series with a defined interval, despite the invasiveness of those methodologies. Also, in cases such as peritoneal metastases that only have non-target lesions, it is impossible to register as clinical trials to examine the effectiveness of chemotherapy and assess the tumor-shrinking effect unless the primary lesion of gastric cancer is regarded as a target lesion. Virtual endoscopic analysis (CT gastrography) can be readily used for imaging of the stomach in elderly or poor risk patients with gastric cancer because of its noninvasiveness and relatively short inspection time. Therefore, we conducted a comparative evaluation of the primary lesions between GS and CT gastrography for post-chemotherapy patients with unresected gastric cancer to probe the possibility of employing CT gastrography as a substitute for GS.

Subjects and methods

Patients

Twenty-three patients were enrolled for this study, and they underwent both GS and 64-channel CT. GS was performed before CT in all patients on different days within 2 weeks. To be eligible for this study, patients were required to be aged 20 years or older and to have histologically proven gastric carcinoma, an endoscopically determined gastric tumor lesion, and Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, and no other active progressive cancer.

CT examination

All the patients were scanned using a 64-channel CT scanner (Aquilion 64; Toshiba Medical Systems Co., Tokyo, Japan) by the gas-extension method. After overnight fasting to empty the stomach, each patient received 20 mg of scopolamine (Buscopan; Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan), or 1 mg of glucagon (Glucagon G Novo; Eisai Co., Ltd., Tokyo, Japan) was injected intramuscularly to relax the bowel wall and reduce peristaltic bowel movement, and they ingested 7.5 g of an effervescent agent (Barosu effervescent granules-S; Horii Pharmaceutical Ind., Ltd., Osaka, Japan) with a small amount of water just before scanning to achieve gastric

pouch distension. Initially, unenhanced CT was performed from the diaphragmatic dome to the renal pedicle at a low dose (less than 100 mA) during a single breath-hold with patients in the prone position after a scout projection had been obtained that showed the gaseous distended stomach. In cases in which a gastric lesion was located at the fundus or cardia, CT was performed with the patient in the right lateral decubitus position. Then, a contrast-enhanced study was performed using biphasic helical CT scanning. Enhancement was achieved with 100–150 ml of non-ionic iodinated monomer solution with a concentration of 300 mgI/ml (Iomeron; Eisai Co., Ltd., Tokyo, Japan) injected at a flow rate of 3.0 ml/s. The total amount of injected contrast material was adjusted according to the body weight of the patients (2 ml/kg).

The CT parameters were: 64-detector configuration, rotation time: 0.5 s, and tube voltage: 120 kVp. Automated tube current modulation (VolumeEC; Toshiba Medical Systems Co., Tokyo, Japan) was routinely used for all patients. CT images were obtained at portal venous phase. CT data acquisition was started 30 s after the trigger threshold (150 HU on the abdominal aorta) had been reached. Patients were instructed to suspend respiration during scanning.

The raw data were transferred to a workstation (ZIOSTATION; Ziosoft, Inc., Tokyo, Japan). Images were retrospectively reconstructed using a 0.5-mm section index. CT gastrographic images were generated by experienced technicians who did not participate in the image analysis. CT volumetry was used to measure the volume of the stomach.

Assessment of response

Pretreatment evaluation included gastroscopy and CT gastrography performed within 2 weeks before the treatment. GS and CT gastrography were performed every two cycles or more as clinically indicated. Patients were considered assessable for response if they had at least one follow-up assessment. GS and CT gastrography were independently analyzed by gastroenterologists in blind fashion. Endoscopic and CT gastrographic assessments of treatment response were based on the JCGC criteria [5] and the RECIST after chemotherapy. Assessments of measurable metastatic target lesions by CT were defined according to RECIST. CT gastrography was compared with GS, which was considered the gold standard.

Statistical analysis

Patient characteristics were compared by Fisher's exact test, χ^2 test, and Mann–Whitney *U* test. *P* values of less than 0.05 were considered to indicate statistical

significance. The weighted kappa coefficient of reliability was used to test the concordance of the tumor response as determined by GS and CT gastrography. We considered a κ value of more than 0.81 to represent almost perfect agreement and values from 0.61 to 0.80, from 0.41 to 0.60, from 0.21 to 0.40, and from 0 to 0.20 to represent substantial, moderate, fair, and slight agreement, respectively. Values less than 0 were considered to represent poor agreement [6].

Results

Characteristics of patients

From April 2008 to August 2011, 23 patients (mean 66.4 years; range 58–80 years) with unresectable advanced (21 patients) and unresected early (2 patients) gastric cancer were enrolled for this study, and they underwent 58 examinations (mean 2.5 times; range 1–11 times). There were 17 (73.9 %) men and 6 (26.1 %) women, with a median age of 66 years (range 58–85 years). Chemotherapy regimens were a DCS regimen (combination of docetaxel, cisplatin, and S-1), SP regimen (S-1 and cisplatin), S-1 monotherapy, paclitaxel monotherapy, and others (Table 1).

Evaluation in accordance with the JCGC, 13th edition

Evaluation was conducted by setting the primary lesion of gastric cancer as the target lesion in accordance with the JCGC, 13th edition. If compared among four groups, i.e., CR/PR/SD/PD (Table 2), GS for the primary lesion of gastric cancer identified CR:PR:SD:PD = 2:18:22:16, whereas CT gastrography identified CR:PR:SD:PD = 0:19:27:12. The accuracy by both methodologies was 77.6 % (45/58) (weighted κ = 0.67, P < 0.01; substantial agreement) (Fig. 1). We probed the potential differences of the results by macroscopic type, histopathological grading, location, and chemotherapy regimen, but no difference was identified (Table 3). Volumetric analysis found no difference between male and female patients (589:441 ml, P > 0.05) and between the existence and nonexistence of esophageal hiatal hernia (469:596 ml, P > 0.05).

Evaluation in accordance with RECIST

Next, we evaluated the primary lesion as the non-target lesion in accordance with RECIST. When compared among three groups, i.e., CR/(non-CR/non-PD)/PD (Table 4), GS for the primary lesion of gastric cancer identified CR:(non-CR/non-PD):PD = 2:40:16. Accuracy

Table 1 Patient characteristics

Patients (examinations)	23 (58)
Median age; years (range)	66.4 (58–85)
Sex	
Male:female	17:6
Number of patients treated with chemotherapy lines	
First-line:second-line or more	20:3
Histopathological grading	
G1+G2:G3+G4	10:13
Macroscopic type	
1:2:3:4	3:9:8:3
Location on three anatomic parts	
U:M:L	7:11:5
Chemotherapy regimen	
DCS:SP:S-1:PTX:others	24:12:10:2:1

Table 2 Evaluation in accordance with the JCGC criteria

CT gastrographic assessment	Gastroscopic assessment			
	CR	PR	SD	PD
CR				0
PR	2	13	2	2
SD		5	20	2
PD				12
	2	18	22	16

was 90.0 % (52/58) (weighted κ = 0.75, P < 0.01; substantial agreement).

Comparison between non-PD and PD groups

In the evaluation of chemotherapy based on RECIST, the distinction between PD and non-PD is important for making the decision about continuing therapy. Therefore, we compared the results of evaluation between non-PD cases and PD cases. The result according to GS was non-PD:PD = 42:16, and the result according to CT gastrography was non-PD:PD = 46:12. If GS was used as the “gold standard,” the sensitivity of CT gastrography was 100 % (42/42), specificity was 75.0 % (12/16), and accuracy was 93.1 % (54/58) (κ = 0.81, P < 0.01; almost perfect agreement). Discordant cases were the case of gastric remnant cancer, the case with insufficient distension of the stomach, the healed case with stenosis and scarring, and the case in which the wrong position had been selected for the examination.

Concordance period by evaluation timing

The average period from PD to first-line chemotherapy in all nine cases assessed was 9.9 months (range 5–18 months). In these cases, the diagnosis of the gastric

Fig. 1 Concordant case. **a** Endoscopic finding before chemotherapy showed type 2 gastric cancer at the lesser curvature of the antrum. **b** Virtual gastrosopic image before chemotherapy. **c** Surface shaded image before chemotherapy. **d** Endoscopic finding after chemotherapy. **e** Virtual gastrosopic image after chemotherapy showed tumor regression to flattened shape, and the response was evaluated as the same result as the endoscopic finding. **f** Surface shaded image after chemotherapy

Table 3 Comparison of concordance rate in characteristics of cancers

Concordance rate (%)		
Borrmann class		
1:2:3:4	77.8 (7/9):69.0 (20/29):92.3 (12/13):85.7 (6/7)	ns (Fisher's exact test)
Histopathological grading		
G1 + G2 (pap, tub1):G3 + G4 (tub2, por, sig)	77.3 (17/22):77.8 (28/36)	ns (χ^2 test)
Location on three anatomic parts		
U:M:L	76.9 (10/13):69.0 (20/29):93.8 (15/16)	ns (Fisher's exact test)
Chemotherapy regimen		
DCS:SP:S-1:PTX	75.0 (18/24):75.0 (9/12):100 (8/8):50.0 (3/6)	ns (Fisher's exact test)

ns Not significant

primary lesions with GS and CT gastrography in two groups of PD and non-PD patients was made at an average period of 7.2 months (range 5–18 months).

Table 4 Evaluation in accordance with RECIST

CT gastrographic assessment	Gastrosopic assessment		
	CR	Non-CR/non-PD	PD
CR			0
Non-CR/non-PD	2	40	4
PD			12
	2	40	16
			58

Discussion

In Japan, the response of gastric cancer to chemotherapy used to be assessed according to the JCGC criteria. However, since the introduction of the 14th edition of the JCGC in 2010, the assessment criteria have conformed to RECIST 1.1. In today's assessment criteria, tumor lesions are regarded as measurable when they can be measured by one-dimensional observation and its diameter is larger than or twice the CT scan thickness. Therefore, the primary lesions of gastric cancer, which used to be evaluated by X-ray scanning or endoscopic observation, are now regarded as non-measurable lesions, hence non-target lesions.

Accordingly, the results of evaluations on primary lesions are regarded as reference opinions only and are described as an appendix. However, the 14th edition of the JCGC also states in its proviso that “the primary lesions are treated as non-target lesions unless they are reproducibly measurable as target lesions with a methodology, such as CT gastrography.” Therefore, if reproducibly measurable, it is possible for us to regard the primary lesions as target lesions. In recent years, the effectiveness of CT gastrography for depicting gastric cancer has been reported [7, 8]. The objectivity of the diagnosis can be sustained because the tumor diameter can be measured by CT gastrography. We probed the possibility of using CT gastrography as a substitute for GS in a post-chemotherapy response assessment by using GS as the gold standard.

We assessed the effectiveness of CT gastrography and GS in accordance with the criteria defined in JCGC, 13th edition, and found the accuracy to be 75.9 % (44/58) for evaluations in four groups of CR/PR/SD/PD. No statistically significant difference in accuracy was identified among some classifications from the analyses on responses and gastric distension either.

Next, we used the ongoing criteria defined in the JCGC, 14th edition, for evaluation. With this evaluation, PR and SD became non-CR/non-PD, and accuracy in three groups of CR/(non-CR/non-PD)/PD was 90.0 % (52/58).

These series of findings proved that a CT gastrography-only approach can achieve an equivalent observation to GS in 90 % of the cases with post-chemotherapy response assessment. Among the six cases in which we found discordant results, two were regarded as CR by GS that were regarded as non-CR/non-PD by CT gastrography, because a complete disappearance of the target lesion was not confirmed by CT gastrography. Four other discordant cases were all caused by insufficient distension of the stomach. The reasons were as follows:

- the local recurrence was not detectable because of deformity and fibrosis of the gastric wall
- the residual fluid and the primary lesion were difficult to distinguish because of insufficient distension of the stomach
- tumor expansion from the remnant to jejunal side was not detected in the case of gastric remnant cancer
- the wrong position was selected for examination

However, when evaluating the response of chemotherapy for making decisions on the choice of therapies, the critical factor is not the best possible efficacy but the controllability of the disease, i.e., the confirmation of non-PD status.

Then, we evaluated the accumulated cases in this study by the two groups, i.e., non-PD cases [CR/(non-CR/non-PD)] and PD cases, and we found 93.1 % accuracy (54/58),

100 % sensitivity (42/42), and 75.0 % specificity (12/16) between CT gastrography and GS. Four discordant cases were the same as the ones observed in the three-group evaluation, i.e., CR, non-CR/non-PD, and PD. The predictive value of non-PD was 93.1 % (42/46) and that of PD was 100 % (12/12). Judging from these findings, CT gastrography has a reliable sensitivity for identifying non-PD status in the post-chemotherapy response assessment, albeit it requires caution because of the possibility of misinterpretation in the case of insufficient distension of the stomach. Also, CT gastrography exhibited 100 % accuracy for identifying PD status. It seems possible that we can make judgments without using GS when CT gastrography returns a PD status.

Next, in the comparison of overall response with or without the evaluation of the primary lesion, the accuracy for the evaluations in four groups of CR/PR/SD/PD was low, whereas that in the two groups of non-PD/PD was approximately 70 %. In the evaluation of overall response, the average concordance periods were 7 months in both groups, which had no significant differences. In the cases in which diagnosed PD groups were not identical, three misinterpretations of overall response as non-PD by CT gastrography were the case with insufficient distension of the stomach, the healed case with stenosis and scarring, and the case in which the wrong position had been selected for the examination, as mentioned before.

According to the results of this study, the concordance periods of the two groups' diagnoses were 7.2 months. The average period to PD of the primary gastric cancer lesion was 9.9 months. From the standpoint of comparing the two groups of non-PD and PD, CT gastrographic evaluation without GS is effective until 7 months from the beginning of chemotherapy, as CT gastrography exhibited sufficient accuracy. However, after 10 months, the number of PD status patients increased. Therefore, CT gastrography can be the primary methodology until 7 months from the start of the chemotherapy. Post 7 months, to assure the accuracy of judgment, it is recommended to use both approaches. These results seemed appropriate since the progression free survival of the S-1 plus cisplatin group in the SPIRITS trial [9], whose evaluation target was metastatic lesion (i.e., not primary lesion), was 6.0 months. Therefore, it is safe to assume CT gastrography is effective to evaluate primary lesions without GS until at least 6 months from the inception of chemotherapy.

The issues to use CT gastrography for the evaluation of chemotherapy are as follows:

First, an insufficient gastric distension could cause misinterpretation. In this study, all four cases of misinterpretation were caused by insufficient distension of the stomach. Among those four misinterpretation cases, two of them were caused by technical reasons such as the residual

fluid in the stomach and the wrong examination position. Another cause was gastric remnant cancer, and the other was the healed case with stenosis and scarring. In those cases, CT gastrography should be applied with caution, because:

- It is difficult to distend the jejunum in a reproducible manner in the case of remnant cancer.
- In the case of stenosis and scarring, the recurrence of wall deformity of the stomach causes insufficient extension of the gastric wall.

In addition, in terms of the reproducibility of CT gastrography, there was no obvious relation between accuracy of evaluation and gastric distension throughout this investigation, but volumetry in every diagnosis enabled us to evaluate the relative degree of distension.

We assessed the validity of CT gastrography. By applying CT gastrography with a careful emphasis on reproducibility, the number of GSs for post-chemotherapy evaluation could be reduced. Also, as CT gastrography may enable us to define the primary lesion of gastric cancer as a target lesion, it would be possible to register cases such as peritoneal metastases in which the metastases have only non-target lesions to phase II clinical trials whose major subject matter is the tumor-shrinking effect. CT gastrography enables us to objectively identify not only the morphologic features of the tumor, but also its size. If we could stabilize the gastric distension in a reproducible manner, the primary lesion could be treated as one of the defined targets.

Conclusions

Although it entails complicated processes for the assessment itself and the analysis to follow, CT gastrography has

proved its reliability by the high accuracy and predictive value of PD of 100 %. The possibility was indicated that CT gastrography can be used as a substitute for GS in post-chemotherapy response evaluation, once conditions, e.g., normalizing the gastric distention, have been met.

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