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ORIGINAL ARTICLE

Diffuse-type gastric cancer: specific enhancement pattern on multiphasic contrast-enhanced computed tomography

Daisuke Tsurumaru[1] · Mitsutoshi Miyasaka[1] · Toshio Muraki[1] · Yoshiki Asayama[2] · Akihiro Nishie[1] · Eiji Oki[3] · Minako Hirahashi[4] · Tomoyuki Hida[4] · Hiroshi Honda[1]

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Abstract
Purpose To evaluate the enhancement pattern of diffuse-type gastric cancers (DGCs) on multiphasic contrast-enhanced computed tomography gastrography (CECTG).
Methods and materials We studied 21 consecutive clinically diagnosed DGC patients who underwent CECTG. Gastric distension was obtained using effervescent granules. CT images were obtained 40 s (arterial phase) and 240 s (delayed phase) after injection of a nonionic contrast material. Two radiologists reviewed the CT images and analyzed layers and enhancement patterns. The readers evaluated the enhancement degree (mild, moderate, or marked) and calculated CT attenuation values by placing circular regions of interest (ROIs) within each layer of the lesion. The CT findings of 11 operated cases were correlated with pathological results.
Results Most lesions were double-layered in the arterial phase, with a moderately enhanced inner layer and a mildly enhanced outer layer, and single-layered in the delayed phase. The mean attenuation value of the inner layer (146 ± 32.8 HU) was significantly higher than that of the outer layer (80.4 ± 15.5 HU) in the arterial phase ($p = 0.0001$). In the pathological analysis, wall stratification was preserved in nine cases and not preserved in two cases.
Conclusion Most DGCs showed a double-layered pattern in the arterial phase and a single-layered pattern with moderate enhancement in the delayed phase.

Keywords Gastric cancer · Multiphasic contrast-enhanced computed tomography · Enhancement pattern

Introduction

Diffuse-type gastric cancer (DGC), also known as "scirrhous carcinoma" or "linitis plastica," is a special type of gastric cancer characterized by diffusely infiltrating lesions that form abundant fibrous stroma as well as poor distensibility of the stomach, depending on the extent of the lesion. Since DGC is at a far-advanced stage when diagnosed, it is often treated with systemic chemotherapy. DGC has the poorest prognosis among all types of gastric cancers, with a 5-year survival rate of approximately 3–10% [1–3].

It is well known that DGC presents diffuse wall thickening on computed tomography (CT). There have also been a few reports of CT findings with regard to DGC using recent multidetector (MD) CT techniques such as three-dimensional (3D) CT gastrography [4–6]. Chen et al. investigated the utility of MDCT in differentiating diseases involving giant gastric folds, and they sought to identify the best imaging predictor of the presence of malignancy in patients with giant gastric folds; they concluded that DGCs tended to show a thickened gastric wall with gradual inner to outer

✉ Daisuke Tsurumaru
tsuru-d@radiol.med.kyushu-u.ac.jp

[1] Departments of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan

[2] Advanced Imaging and Interventional Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan

[3] Surgery and Sciences, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan

[4] Anatomic Pathology and Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan

good transmural enhancement from the arterial phase to the delayed phase on dynamic contrast-enhanced CT [7].

The purpose of the present study was to analyze the CT findings including the enhancement pattern of DGC on multiphasic contrast-enhanced CT gastrography (CECTG).

Materials and methods

Patient population

This retrospective study was approved by the institutional review board of our institution, and the requirements for informed consent were waived. From September 2006 to December 2015, 21 consecutive patients with DGC who were evaluated by CECTG before treatment were enrolled in our study. DGC was defined based on medical records of endoscopy or fluoroscopy, the findings of which were as follows: an infiltrating tumor sparing the superficial mucosal layer with no bulky intraluminal mass or prominent ulcer [8]. DGC and Borrmann type 4 cancer were the same entity in this work. The subjects were seven males and 14 females whose median age was 65. All cases were histologically proven poorly differentiated adenocarcinomas. Patients who underwent previous gastrectomy were excluded. The tumor stages were stated on the patients' operation records according to the Japanese Classification of Gastric Carcinoma (3rd English edition) [8]. The patients' characteristics are compiled in Table 1.

Table 1 Patients' characteristics

Characteristic	Value
Age (years; median, range)	65 (31–92)
Males:females	7:14
Histology	
Poorly differentiated adenocarcinoma	21
Clinical stage	
II	9
III	5
IV	7
T stage (operated cases)	
T3	1
T4a	10
Treatment (initial)	
Surgery	11
Chemotherapy	10

CT protocol

Computed tomography was performed using two CT scanners: a 64-detector row CT (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan; $n = 7$) and a 320-detector row CT (Aquilion ONE; Toshiba Medical Systems; $n = 14$). The scan parameters were as follows: for the 64-detector row CT scanner: rotation time 0.5 s, section thickness and intervals 1 mm, beam collimation 1 mm, pitch 53, 120 kVp, 200 mAs, and matrix 512 × 512; for the 320-detector row CT scanner: rotation time 0.5 s, section thickness and intervals 0.5 mm, 120 kVp, 200 mAs, and matrix 512 × 512.

After an overnight fast, each patient ingested 5.25 g of an effervescent agent (Baros Effervescent Granules-S; Horii Pharmaceutical Industries, Saitama, Japan) with a small amount of water just before the scanning to achieve gastric pouch distension. The patient was then given an intramuscular injection of 20 mg of scopolamine (Buscopan; Boehringer Ingelheim, Ingelheim am Rhein, Germany) to suppress peristalsis. The scanning covered the entire stomach during a single breath-hold.

Computed tomography images were obtained 40 s (arterial phase), 70 s (portal phase), and 240 s (delayed phase) after an infusion of 2 mL/kg of nonionic contrast material (Iopamiron370; Bayer Health Care, Osaka, Japan) at a rate of 3 mL/s. The patient's position was supine in all phases. The CT imaging data for the arterial and delayed phases were transferred to a commercially available workstation equipped with image reconstruction software (Synapse Vincent, Fujifilm, Tokyo) for image analysis.

CT image analysis

The CT images were interpreted by consensus by two gastrointestinal abdominal radiologists with 9 and 15 years of experience in gastrointestinal imaging) using optical endoscopic and/or fluoroscopic findings as a reference. They reviewed multiplanar reconstruction (MPR) images and axial images for each case. The lesion was classified as cancerous when the gastric wall showed thickening of ≥ 6 mm [9].

For the MPR image analysis, the readers calculated the long-axis tumor length and the maximum thickness of the most thickened gastric wall, and they evaluated the maximum circumference involvement in the short-axis dimension. For the axial image analyses, the readers evaluated the homogeneity and the layer pattern of the thickened gastric wall of the largest tumor section on axial images as being representative of the arterial and delayed phases. When the lesion showed a multilayered pattern, or even when the lesion showed a single-layered pattern, the readers evaluated the degree of enhancement and measured the CT attenuation for each layer.

The degree of enhancement was subjectively assessed and categorized as follows: mild when the enhancement

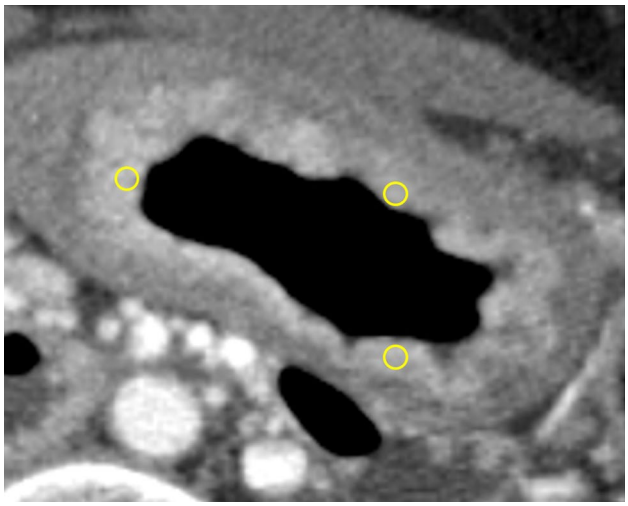

Fig. 1 Measurement of CT attenuation values. This case shows circumferential gastric wall thickening with a double-layered pattern in the arterial phase on an axial image. Three circular ROIs were drawn in the inner layer to measure attenuation values

was similar to that of the adjacent muscle; moderate when the enhancement was higher than that of the muscle but lower than that of blood vessels; and marked when the enhancement was approaching that of blood vessels. The readers then measured the attenuation value by placing circular regions of interest (ROIs) within each layer of the lesion. The ROIs were placed in three different areas of each layer, and the mean of the three mean attenuation values of the ROIs was calculated (Fig. 1).

Pathological analysis

Eleven resected cases were analyzed pathologically. Two pathologists reviewed the pathological specimen and in consensus determined the histological type, stromal volume, and infiltrative pattern according to the Japanese Classification of Gastric Carcinoma (3rd English edition). The stromal volume was classified into three grades as follows: medullary type (med): scanty stroma; scirrhous type (sci): abundant stroma; intermediate type (int): the quantity of stroma is intermediate between the two other types. The infiltrative pattern was classified into three grades as follows: INFa tumor displays expanding growth with a distinct border with the surrounding tissue; INFb tumor shows an intermediate pattern between INFa and INFc; INFc tumor displays infiltrative growth with no distinct border with the surrounding tissue [8]. They also subjectively evaluated whether the stratification of the involved gastric wall was preserved, based on the histopathological structure evaluated above.

Table 2 CT findings

Variable		
Tumor length (mm)	99.5 (82.7–187.1)	
Maximum thickness (mm)	13.8 (8.2–25.0)	
Circumference involvement (d)		
0–90	3	
91–180	1	
181–270	1	
271–360	16	
Homogeneity	Arterial phase	Delayed phase
Homogeneous	21	21
Heterogeneous	0	0
Layer pattern		
Single-layered	0	18
Double-layered	21	3

Statistical analysis

We used a paired *t* test to compare the CT attenuation values and used a McNemar test to compare the degrees of enhancement of the layers in each case. Differences with p values <0.05 were considered significant. The statistical analyses were performed using SPSS 21.0 for Windows software (SPSS, Chicago, IL, USA).

Results

In the MPR image analysis, the median long-axis tumor length was 99.5 mm and the median maximum thickness was 13.8 mm. The maximum circumference involvement was full in 16 cases and non-full in the other five cases. In the axial image analysis, all lesions showed homogeneous gastric wall thickening in both the arterial and delayed phases.

Regarding the layer pattern, all lesions were observed to be double-layered in the arterial phase. In the delayed phase, 18 lesions were single-layered and three were double-layered (Table 2). The degree of enhancement was marked ($n = 4$) to moderate ($n = 17$) for the inner layer and mild ($n = 21$) for the outer layer in the arterial phase ($p = 0.0001$). The degree of enhancement was moderate ($n = 21$) for the inner layer and moderate ($n = 18$) to mild ($n = 3$) for the outer layer in the delayed phase ($p = 0.8012$) (Table 3).

In the CT attenuation measurements, the mean attenuation value of the inner layers (146 ± 32.8 HU) was significantly higher than that of the outer layers (80.4 ± 15.5 HU) in the arterial phase ($p = 0.0001$). There was no significant difference between the attenuation values of the inner

Table 3 Degree of enhancement

	Inner layer	Outer layer	*p* value
Arterial phase			
Mild	0	21	0.0001
Moderate	17	0	
Marked	4	0	
Delayed phase			
Mild	0	3	0.8012
Moderate	21	18	
Marked	0	0	

Table 4 CT attenuation values

	Inner layer	Outer layer	*p* value
Arterial phase	146.9 ± 32.8	80.4 ± 15.5	0.0001
Delayed phase	126.3 ± 20.9	121.7 ± 15.9	0.0867

Data are the mean attenuation values in Hounsfield units, with standard deviations

(126.3 ± 20.9 HU) and outer (121.7 ± 15.9 HU) layers in the delayed phase ($p = 0.0867$) (Table 4).

In the pathological analysis of 11 resected cases, histological types were poorly differentiated adenocarcinoma in six cases and that combined with signet ring cell carcinoma in five cases. The stromal volume and infiltrative pattern were sci and INFc for all cases. Wall stratification was preserved in nine cases and not preserved in two cases (Table 5). A representative case is shown in Fig. 2.

Discussion

This may be the first study to analyze the CECTG features of diffuse-type gastric cancers (including enhancement patterns) in detail. In our series, the DGCs showed diffusely extensive growth (e.g., from the upper to the lower stomach region) according to our results. DGCs have a unique infiltrative growth pattern along the submucosal layer without a prominent mucosal mass or ulcer, and the cancer cells are often widely scattered within a dense fibrous stroma from an associated desmoplastic reaction and spare the mucosal layer [4, 10–13]. Kim et al. analyzed the extent of longitudinal tumors and the type-specific diagnosis of Borrmann type IV gastric cancer using CT and gastroscopy, and pathology revealed that only 13% of them were localized within a single site [14].

Regarding enhancement patterns, all 21 of the DGCs in the present analysis showed double-layered or single-layered homogeneous wall thickening with contrast enhancement. In the subjective analyses by the two readers, most of the lesions were double-layered with a moderately enhanced inner layer and a mildly enhanced outer layer in the arterial phase, and they were single-layered in the delayed phase, as confirmed by the objective CT attenuation value measurements.

It is generally considered that most gastric cancers show moderate to marked enhancement in the early phase on contrast-enhanced CT [15–19]. However, gastric cancers may have various enhancement patterns because they have diverse pathological factors including cell differentiation, the amount of fibrous stroma, and the infiltrative pattern. We previously analyzed the enhancement patterns of early gastric cancers with ulceration by using dynamic contrast-enhanced CT; we found that the early gastric cancers with ulceration contained varying degrees of fibrous tissue associated with ulceration, and that most of the lesions had low attenuation values in the arterial and portal phases and had peak enhancement in the delayed phase [20].

Intratumoral fibrous stroma may be one of the most important of the factors that affect the enhancement patterns of DGCs, as is peritumoral fibrous stroma for early gastric cancer with ulceration. Lee et al. reported that most of the signet ring cell carcinomas examined showed diffusely infiltrative growth of malignant cell groups intermingled with immature and mature fibrosis. The mature scar (fibrosis) was composed mainly of dense collagen fibers but only a few cells and vessels, whereas the early or immature fibrosis contained abundant fibroblasts and neovascularity. Subsequently, mature fibrosis shows poor contrast enhancement, whereas early or immature fibrosis shows good contrast enhancement in the portal phase [5, 21]. Takao et al. reported that gastric cancers composed of marked fibrous tissue stroma can show gradual enhancement on triphasic CT [22].

Based on our results, we speculate that the double-layered pattern of DGCs can be attributed to the infiltrative spread of tumor cells and associated fibrous stroma that preserve the stratification of the involved gastric wall. Several authors have reported that most scirrhous carcinomas of the stomach show gastric wall thickening that preserve wall stratification on ultrasonography, which is well correlated with histopathological findings for resected specimens [23, 24]. A normal gastric wall shows a single- or double-layered pattern on CECTG using the gas-distension method according to a previous study. The CT attenuation value of the inner half of the normal gastric wall corresponding to the mucosal–submucosal layer (mostly comprising the submucosal vascular plexus) is higher than the outer half corresponding to the muscular–serosal layer [25]. We also speculate that a marked to moderately enhanced inner layer corresponds to enhancement of the mucosa, muscularis

Table 5 Radiological–pathological correlation for resected cases ($n = 11$)

Age	Sex	Stage	Arterial phase					Delayed phase					Pathology			
			Layer pattern	Degree of enhancement		CT attenuation value (HU)		Layer pattern	Degree of enhancement		CT attenuation value (HU)		Histological type	Stromal volume	Infiltrative pattern	Wall stratification
				Inner layer	Outer layer	Inner layer	Outer layer		Inner layer	Outer layer	Inner layer	Outer layer				
52	M	IIIA	Double-layered	Marked	Mild	152.3	93.1	Single-layered	Moderate	Moderate	127.2	118.9	Por	Sci	INFc	Not preserved
78	M	IIIC	Double-layered	Moderate	Mild	104.8	57.2	Double-layered	Moderate	Mild	128.8	108.5	Por + sig	Sci	INFc	Preserved
49	F	IV	Double-layered	Moderate	Mild	156.9	94.4	Single-layered	Moderate	Moderate	102.3	112.3	Por	Sci	INFc	Preserved
67	M	IV	Double-layered	Moderate	Mild	117.8	74.8	Double-layered	Moderate	Mild	116.8	91.3	Por	Sci	INFc	Preserved
92	F	IV	Double-layered	Marked	Mild	179.8	67.1	Single-layered	Moderate	Moderate	132.3	121.9	Por	Sci	INFc	Preserved
55	F	IIIC	Double-layered	Marked	Mild	228.4	98.7	Single-layered	Moderate	Moderate	166.8	155.6	Por + sig	Sci	INFc	Preserved
39	F	IV	Double-layered	Moderate	Mild	202.7	108.3	Single-layered	Moderate	Moderate	112.3	124.8	Por	Sci	INFc	Preserved
51	F	IIIA	Double-layered	Moderate	Mild	141.9	90.1	Single-layered	Moderate	Moderate	132.2	120.5	Por + sig	Sci	INFc	Not preserved
69	F	IIIC	Double-layered	Moderate	Mild	127.1	83.4	Single-layered	Moderate	Moderate	143.4	136.0	Por	Sci	INFc	Preserved
68	M	IIIC	Double-layered	Moderate	Mild	112.2	93.6	Single-layered	Moderate	Moderate	95.2	106.7	Por + sig	Sci	INFc	Preserved
74	F	IV	Double-layered	Moderate	Mild	110.9	55.6	Single-layered	Moderate	Moderate	139.7	142.9	Por + sig	Sci	INFc	Preserved

Por poorly differentiated adenocarcinoma, *sig* signet ring cell carcinoma

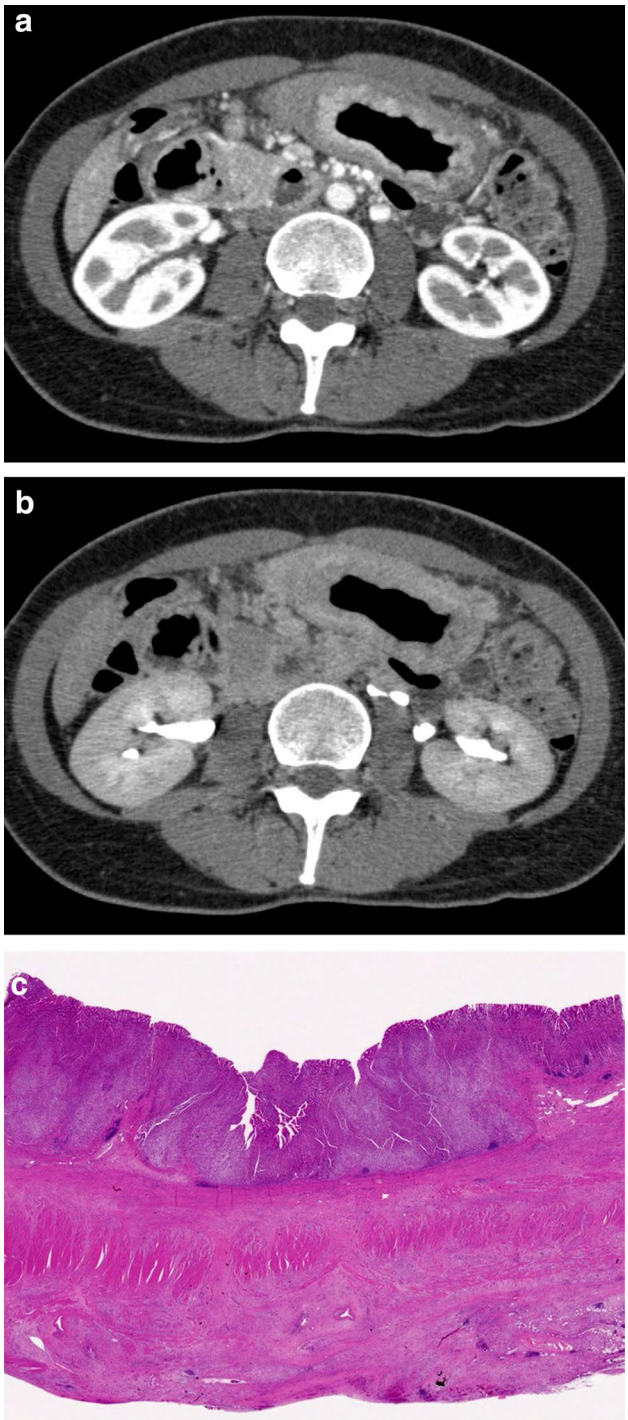

Fig. 2a–c DGC in a 39-year-old woman. CE-CTG shows homogeneous wall thickening of the gastric body involving the full circumference. **a** The lesion shows a double-layered pattern with a markedly enhanced inner layer (202.7 HU) and mildly enhanced outer layer (95.3 HU) in the arterial phase. **b** The lesion shows a single-layered pattern with moderate enhancement (112.3 HU for the inner layer and 118.2 HU for the outer layer) in the delayed phase. **c** A photomicrograph shows a proliferation of poorly differentiated adenocarcinoma cells with abundant fibrous stroma infiltrating an entire layer of the stomach and preserving wall stratification

mucosa, and thickened submucosa (including the submucosal vascular plexus) as well as cancer cell infiltration with fibrous stroma, while a mildly enhanced outer layer corresponds to enhancement of the thickened muscular and serosal layer, again with cancer cell infiltration with fibrous stroma.

Because DGCs grow infiltratively and predominantly in the submucosa and have the same appearance as the overlying mucosa, endoscopists often have difficulty recognizing the DGC [26, 27]. The positive rate for cancer diagnosis on endoscopic biopsy is significantly lower in DGC cases than for other types of gastric cancers [28, 29]. In addition, gastroscopy has shown limited utility for determining tumor extent in patients with DGC [11, 13, 29]. In contrast, CT could allow radiologists to correctly diagnose the tumor extent in DGC, even in cases of pyloric stenosis in which a gastroscope cannot be advanced [14]. Our results highlight the idea that the specific enhancement pattern of DGCs could aid the diagnosis of tumor extent or invasion depth as well as tumor localization.

It is also important to differentiate DGCs from other gastric malignant tumors that cause diffuse wall thickening in the stomach, such as malignant lymphomas. Chen et al. reported that malignant lymphomas (large B cell lymphomas) show diffuse bulky thickening of the gastric wall and intermediate enhancement of the thin, preserved mucosal layer in the late arterial phase, while intermediate enhancement of the bulky tumor mass is evident in all phases on dynamic MDCT, which is different from the DGC enhancement pattern seen in our study [7].

Our study had several limitations. First, it was a single-institution study with a small sample size. Second, only half of the samples were evaluated pathologically after operation. There was no radiological–pathological correlation for another 10 patients who underwent chemotherapy. Third, this study did not compare the CT findings for DGCs with those for non-diffuse-type gastric cancers, which could be used to determine whether the CT findings presented above are specific. Fourth, all of the cases in our series underwent the specific protocol of CECTG. It is unclear whether our results are helpful for patients who undergo conventional CT protocols.

Conclusions

Our findings suggest that DGCs tend to demonstrate homogeneous wall thickening, and that DGCs tend to be double-layered in the arterial phase, with a moderately enhanced inner layer and a mildly enhanced outer layer, and to show a moderately enhanced single layer in the delayed phase.

These specific CT enhancement patterns may aid the detection of DGCs as well as the estimation of tumor localization or extent.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest associated with this manuscript other than the above grant. This study was approved by the institutional review board of our institution.

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