

Differentiation of Advanced Gastric
Carcinoma with Signet Ring Cell
Carcinoma and Non-Signet Ring Cell
Carcinoma Using Multidetector CT

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Written by writer

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Abstract

Differentiation of advanced gastric carcinoma with signet ring cell carcinoma and non-signet ring cell carcinoma using multidetector CT

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Gastric cancer with signet ring cell histology has been classically characterized by cells containing a sufficient intracytoplasmic volume of mucin to compress the nucleus against the periphery of the cell. Although studies of the prognosis of gastric SRC are not consistent, SRC has been considered to be a poor prognostic factor. The purpose of our study was to assess the capability of MDCT to assist in the differentiation between gastric cancer with SRC and that with NSRC, with a focus on the thickened stomach wall itself.

We retrospectively reviewed MDCT results in 80 patients with pathologically proven AGC with SRC(n=35) and NSRC(n=45). MDCT images of 80 patients were analyzed retrospectively on gross appearance of thickened gastric wall(polypoid/ fungating/ ulcerative/ diffuse infiltrative), predominantly thickened layer(inner/outer), contrast-enhancement pattern(non-layered/ layered) and degree of enhancement(high/moderate/low). And we correlated the CT findings with the histopathologic findings by means of a layer-to-layer comparison.

The most common type of gross appearance in both carcinomas was fungating and the more common contrast enhancement pattern in both carcinomas was a non-

layered pattern. The predominantly thickened layer was a high attenuation inner layer in both carcinomas. High degree contrast enhancement was more common in AGC with SRC(37.1% of patients) than AGC with NSRC(15.6% of patients). In SRC with histopathological review, the groups of malignant cells and immature fibrosis enhance well whereas mature fibrosis shows poor enhancement.

It was difficult to distinguish AGC with SRC from that with NSRC based on the MDCT findings of the thickened stomach wall alone. But, high degree contrast enhancement was more common in AGC with SRC than AGC with NSRC.

Key words : stomach, CT, gastric cancer, singet ring cell carcinoma

Differentiation of advanced gastric carcinoma with signet ring cell carcinoma and non-signet ring cell carcinoma using multidetector CT

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I. Introduction

Gastric cancer with signet ring cell histology has been classically characterized by cells containing a sufficient intracytoplasmic volume of mucin to compress the nucleus against the periphery of the cell^{1,2}. Gastric cancer with signet ring cell carcinoma(SRC) is characterized by its potential to diffusely infiltrate the gastric wall and to cause a marked scirrhous reaction^{1,2}. SRC of stomach appears to occur at a higher frequency in females and young patients^{1,3}. Although studies of the prognosis of gastric SRC are not consistent, SRC has been considered to be a poor prognostic factor^{1,3-8}. Therefore, it is clinically useful to differentiate gastric cancer with SRC from that with non-signet ring cell carcinoma(NSRC).

In the past, the primary role of CT in patients with gastric cancer is to assess the

presence and extent of extragastric spread of tumor to facilitate decisions about optimal therapeutic strategy⁹. Helical CT combined with rapid infusion of intravenous contrast medium and gastric water filling have been used to overcome the limitation of conventional CT in the evaluation of the transmural and extraserosal spread of disease¹⁰. Moreover, multidetector computed tomography (MDCT) offers new opportunities for imaging of gastric disease with higher spatial and contrast resolution than single-section helical CT¹¹.

Recently, Park et al¹² reported that helical CT with adequate distension of stomach by water might help in distinguishing mucinous from nonmucinous gastric carcinoma, primarily on the basis of the enhancement pattern, predominant layer of thickened wall, and gross appearance.

To our knowledge there have been no previous reports comparing the MDCT findings of SRC and NSRC. The purpose of our study was to assess the capability of MDCT to assist in the differentiation between gastric cancer with SRC and that with NSRC, with a focus on the thickened stomach wall itself.

II. Materials and Methods

1. Patient Selection

By performing a computerized search of medical records, we identified 182 patients with a diagnosis of gastric cancer with SRC who underwent surgery at two institutions between January 2003 and March 2004. Pathologic diagnosis of SRC was made when gastric adenocarcinoma was composed of predominantly (more than 50%) small groups of isolated malignant cells containing intracellular mucin². Nine patients with mucinous gastric carcinoma that contained more than 50% of the extracellular mucin were excluded. For comparison with the SRC gastric cancer group, we identified 142 patients with a diagnosis of NSRC gastric cancer who underwent surgery between the same periods at a single institution. Because CT has limitations in the detection of early gastric cancer (EGC) especially in the absence of thickening of the gastric wall, we excluded 179 EGC patients (EGC with SRC: 106 patients, EGC with NSRC: 73 patients). Patients were further excluded from the two groups if pre-operative MDCT images had not been obtained in our two institutions or adequate distention of the stomach by water filling had not been performed. Thus, our retrospective study population included 35 patients (16 men, 19 women; mean age, 53.8 years; age range, 21-78 years) of AGC with SRC and 45 patients (28 men, 17 women; mean age, 55.8 years; age range, 32-78 years) of AGC

with NSRC. The institutional review boards at the two hospitals did not require their approvals or informed patient consent for review of the medical records, files, and images.

2. CT Technique

CT was performed with a 16-channel MDCT(Somatom Sensation 16, Siemens, Forchheim, Germany) or 4-channel MDCT(LightSpeed, General Electric Medical Systems, Milwaukee, Wis). The patients fasted for at least 6 hours prior to the examination. Each patient ingested 600-1000 ml of water immediately before lying on the scanning table. No anti-cholinergic agents or glucagon was administered. After pre-contrast enhancement scanning was performed, a contrast-enhanced CT scan was obtained.

Using 16-channel MDCT, acquisition of arterial phase scans was initiated within 15 seconds after reaching enhancement of the thoracic aorta up to 100 Hounsfield Units as measured using a bolus-tracking technique after intravenous injection of 150 ml of iopromide(Ultravist 300; Schering, Berlin, Germany) or iohexol(Omnipaque 300, Nycomed, Princeton, NJ) through an 18-gauge angiographic catheter inserted into an antecubital vein using a power injector at a rate of 3 ml/s. CT acquisitions were performed in the portal venous phase(start delay of 70 seconds). Arterial phase and the portal venous phase CT images were obtained

by using the following protocol: detector collimation of 5x1.5, rotation time of 0.5 second, table feed of 12 or 24mm per rotation, section width of 5mm, reconstruction increment of 5mm as 5mm-thick sections, 120 kVp, and 160 mAs. The scanning range included only the liver and stomach for the precontrast and arterial phase and the upper abdomen to the iliac crest for the portal venous phase.

With use of 4-channel MDCT, the arterial and the portal venous phase CT images were obtained by using the following protocol: section width of 5mm, reconstruction interval of 3.75mm, a pitch of 1.5:1, 120 kVp, and 240 mAs.

In some cases, images of arterial phase were not obtained, so we evaluated only the CT images obtained during the portal phase.

3. Imaging and Histopathologic Analyses

Two board-certified abdominal radiologists collectively and retrospectively reviewed the MDCT scans obtained in the 80 patients by consensus, without knowledge of the pathologic subtype of the gastric carcinoma. The gross appearance, predominantly thickened layer, contrast-enhancement pattern, degree of contrast-enhancement and the ratio of high-attenuating inner layer thickness to total thickness were evaluated. Gross appearance was classified as one of four types: (a) polypoid, defined as an intraluminal growing mass; (b) fungating, defined as a lesion with a focal wall thickening of more than 1 cm, with or without a depressed area; (c)

ulcerated, defined as a depressed lesion with a wall thickening of less than 1 cm; or (d) diffusely infiltrative, defined as a lesion involving more than 50% of the entire stomach wall. We modified the Borrmann classification of advanced gastric carcinoma to adjust for the appearance of the tumors on CT scans¹². The contrast-enhancement patterns on post-contrast CT images were classified as (a) non-layered or (b) layered, which was defined as diffuse thickening of the gastric wall with more than 50% preservation of a multilayered pattern. The degree of enhancement was graded as follows: (a) high, or tumor attenuation higher than that of the liver; (b) moderate, or tumor attenuation between that of the liver and that of muscle; or (c) low, or tumor attenuation lower than that of muscle. The thickness of the tumor was measured at the thickest point of the most thickened wall, and the predominant thickened layer (high attenuating inner layer or low attenuating middle/ outer layer) was recorded. The ratio of high-attenuating inner layer thickness to total thickness was also calculated. If the high attenuating layer occupied the entire thickness of the gastric wall, the ratio was calculated as 1.00. Other associated findings, such as calcification, also were evaluated.

Four clinicopathologic features (age, sex, T-stage and N-stage) were compared between AGC with SRC to that with NSRC.

The histopathologic findings in surgical specimens from 18 patients (SRC, 12 patients; NSRC, 6 patients) were retrospectively reviewed by two pathologists with

special emphasis on the cellular composition of the thickened gastric wall, the amount and maturity of fibrosis and any other frequent findings. The maturity of fibrosis was graded as mature or immature on the basis of both the density of collagen fibers and the fibroblastic cellular activity.

One radiologist and two pathologists correlated the CT findings with the histopathologic findings by means of a layer-to-layer comparison.

The χ^2 tests were employed for comparing the gross appearances, contrast enhancement pattern, degree of contrast enhancement and predominantly thickened layer of AGC with SRC to that of NSRC. The total thickness of the tumors and the ratio of high-attenuating inner layer thickness to total thickness were compared between SRC and NSRC by means of the Student's t-test. The clinicopathologic features (age, sex, T-stage and N-stage) were also compared between AGC with SRC to that of NSRC by means of the Student's t-test and χ^2 test. A P value of less than 0.05 was considered to indicate a statistically significant difference.

III. Results

The CT imaging features of AGC with SRC and that with NSRC are summarized in Table 1.

The most common type of gross appearance in both carcinomas at CT was fungating : 22(62.9%) of 35 patients with AGC with SRC and in 28(62.2%) of 45 patients with NSRC(Figure 1, 2). The second most common type was diffuse infiltrative in AGC with SRC[n= 7 of 35 patients(20%)](Figure 3) whereas that of NSRC was the ulcerated type[n= 8 of 45 patients(17.8%)]. The difference in gross appearance on CT scan was not significantly different(P = 0.74).

The predominantly thickened layer was a high attenuation inner layer in both carcinomas(Figure 1-4): It occurred in 62.9% of AGC with SRC and in 75.6% of AGC with NSRC. There was no statistically significant difference on the predominantly thickened layer(P = 0.22).

The contrast enhancement patterns in AGC with SRC were the non-layered pattern in 24 of 35 patients(68.6%) (Figure 1) and the layered pattern in 11 of 35 patients(31.4%), with the non-layered pattern in 32 of 45 patients(71.1%) (Figure 2, 4) and the layered pattern in 13 of 45 patients(28.9%) in AGC with NSRC. The contrast enhancement patterns were not significantly different(P = 0.81).

Table 1. Comparison of CT Imaging Features of AGC with SRC Histology and NSRC

Imaging Features		Pathology		
		SRC (n=35)	NSRC (n=45)	P-value
Gross appearance	Polypoid	1	3	
	Fungating	22	28	
	Ulcerated	5	8	
	Diffuse	7	6	0.74
Predominantly thickened layer	Inner	22	34	
	Outer	13	11	0.22
Contrast enhancement pattern	Non-layered	24	32	
	Layered	11	13	0.81
Degree of enhancement	Low	8	5	
	Moderate	14	33	
	High	13	7	0.01

SRC = signet ring cell carcinoma

NSRC = non-signet ring cell carcinoma

The majority of AGC with SRC show a moderate degree[n= 14 patients(40.0%)] or high degree[n= 13 patients(37.1%)] of contrast enhancement(Figure 1). However, the majority of AGC with NSRC show a moderate degree of contrast enhancement[n=33 patients(73.3%)] (Figure 2). There was a statistically significant difference in the degree of contrast enhancement(P = 0.01).

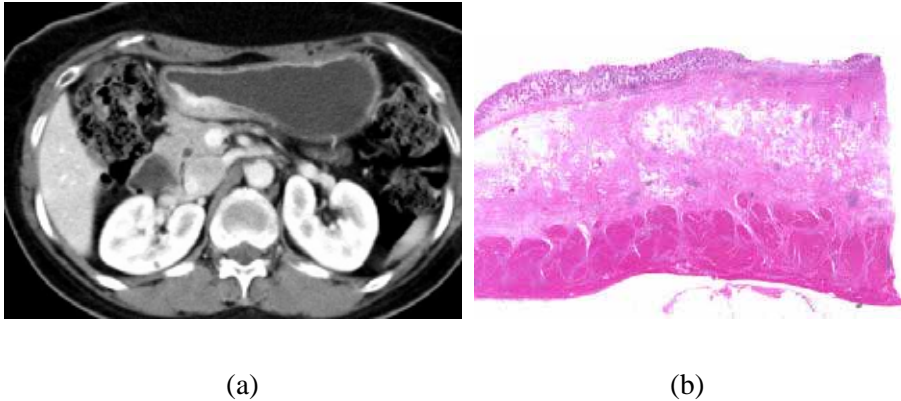


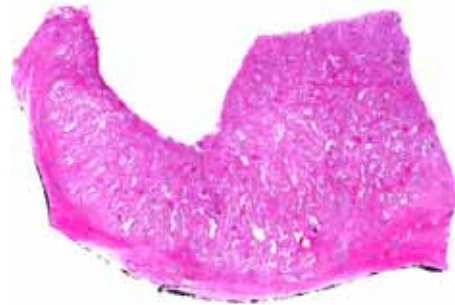
Figure 1. Fungating signet ring cell carcinoma in a 51-year-old woman.

(a) Contrast enhanced CT scan shows focal gastric wall thickening of mainly in the strongly enhancing inner layer. The attenuation of the enhancing thickened inner layer is higher than that of the liver. The inner half of the thickened gastric wall is higher than outer half of the thickened gastric wall.

(b) Low-power photomicrograph shows infiltration of signet ring cells into the muscle layer without mucin pool formation. Inner half of the gastric wall shows ulceration with infiltration of signet ring cells mixed with loose immature fibrosis and outer half of the gastric wall shows dense fibrosis and muscle layer.



(a)



(b)

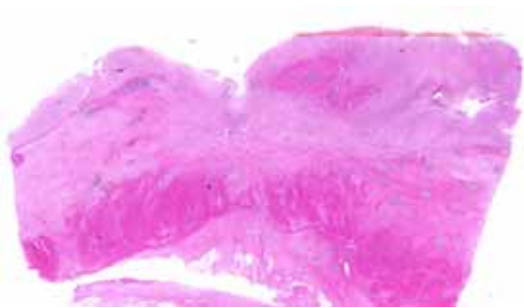
Figure 2. Fungating non-signet ring cell carcinoma in a 70-year-old man.

(a) Contrast enhanced CT scan shows focal gastric wall thickening mainly of the enhancing thickened inner layer. The homogeneous enhancement pattern is shown.

(b) Low-power photomicrograph shows malignant cell groups that have almost replaced the entire stomach wall, with extension into the muscle layer.



(a)

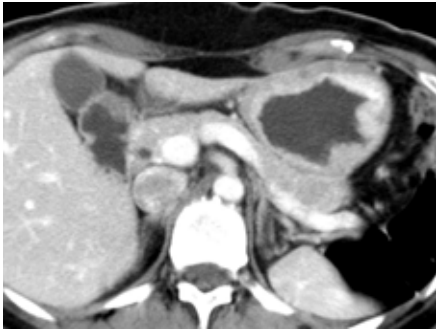


(b)

Figure 3. Diffuse infiltrative signet ring cell carcinoma in a 45-year-old man.

(a) Contrast enhanced CT scan shows diffusely thickened gastric wall with diffuse enhancement. The inner half of the thickened gastric wall is higher than outer half of the thickened gastric wall.

(b) Low-power photomicrograph shows infiltration of malignant cells into the muscle and serosa without mucin pool formation. Signet ring cells have almost replaced the mucosal layer and dense fibrosis in the submucosal to serosal layer.



(a)



(b)

Figure 4. Diffuse infiltrative non-signet ring cell carcinoma in a 43-year-old woman.

(a) Contrast enhanced CT scan shows diffusely thickened gastric wall with enhancement mainly of the inner layer. The attenuation of the enhancing thickened inner layer is higher than that of the liver.

(b) Low-power photomicrograph shows malignant cell groups that have almost replaced the mucosal layer. Dense fibrosis is seen at the submucosal, muscular, and serosal layer.

The tumor thickness of the AGC with SRC ranged from 7.9mm to 24.8mm(mean, 13.9mm) and that with NSRC ranged from 7.0mm to 23.7mm(mean, 14.6mm). Differences in tumor thickness were not statistically significant($P = 0.40$). The ratio of high-attenuating inner layer thickness to total thickness was higher in the AGC with NSRC(range, 0.13-1.00; mean, 0.60) compared to that with SRC(range, 0.17-1.00; mean, 0.50) without a statistically significant difference($P = 0.12$). Calcification in thickened gastric wall was not seen in all of the cases with the AGC with SRC or AGC with NSRC.

The clinicopathological features(age, sex, T-stage and N-stage) between AGC with SRC and NSRC are summarized in Table 2. There were no statistically significant differences between groups in terms of age, sex, T-stage and N-stage.

Table 2. Clinicopathologic features between AGC with SRC Histology and NSRC

Clinicopathologic Features	Pathology		P-value
	SRC (n=35)	NSRC (n=45)	
Age(mean age)	53.8	55.8	0.54
Sex			
Male	16	28	
Female	19	17	0.14
T-Stage			
T2	10	19	
T3	24	26	
T4	1	0	0.24
N-Stage			
N0	11	12	
N1	5	17	
N2	7	7	
N3	12	9	0.12

SRC = signet ring cell carcinoma

NSRC = non-signet ring cell carcinoma

IV. Discussion

The World Health Organization(WHO) classifies gastric carcinoma into four types – (a) papillary, (b) tubular, (c) mucinous, and (d) signet ring cell carcinoma². SRC and mucinous adenocarcinoma of the stomach were confounded as “mucoïd carcinoma” until 1964, because both carcinomas were both characterized by abundant mucus-secretion⁷. WHO defines singet ring cell gastric carcinoma as “an adenocarcinoma more than 50% of the tumor consists of isolated or small groups of malignant cells containing intracytoplasmic mucin”, whereas mucinous adenocarcinoma, by definition, is an adenocarcinoma more than 50% of the tumor contains extracellular mucin pools². In SRC, the tumor cells have five morphologies and these cell types overlap with one another and constitute varying tumor proportions². The characteristics of SRC are its potential to diffusely infiltrate the gastric wall, to cause a marked scirrhus reaction, and to be associated with a poor prognosis¹. Kim et al⁵ have reported that the prognosis for patients with advanced SRC was significantly worse than that for patients with other types of advanced gastric carcinoma. This may be explained by advanced gastric SRC having a larger tumor size, more lymph node metastasis, a deeper invasive depth, and more Borrmann type IV lesions than other histologic types⁵. On the other hand, some studies have reported that patients with advanced gastric SRC had a prognosis similar to that of patients with other types of gastric carcinoma⁶. Although studies of

the prognosis of gastric SRC have not been consistent, SRC has been generally been considered a poor prognostic factor along with mucinous adenocarcinoma^{5,7,8,13}. The survival rate for both SRC and mucinous adenocarcinoma is extremely low⁷. Thus, it is clinically useful to differentiate gastric cancer with mucinous and SRC types from that with other types of gastric carcinoma. Recently, it has been reported that mucinous adenocarcinoma may be distinguished from nonmucinous adenocarcinoma primarily on the basis of the thickened stomach wall itself, on helical CT scan¹². To our knowledge, there have been no reports of a comparison of the MDCT findings of SRC versus NSRC. Therefore, we evaluated whether SRC also could be differentiated from NSRC on MDCT.

In our study, the most common type of gross appearance in both carcinomas by CT imaging was fungating. The second most common type was ulcerated in NSRC and diffuse infiltrative in SRC. A diffusely infiltrative gross appearance was seen more often in AGC with SRC(20.0%) than AGC with NSRC(13.3%), a non-statistically significant difference. The result was concordant with the previous report that Borrmann type III (ulcerative, 62.3%) was most common in AGC with SRC and type IV (diffuse infiltrative, 26.8%) was the second most common pattern⁵. The proportion of Borrmann type IV lesions in AGC with SRC was significantly higher than other cell types⁵. This finding may arise from the ability of SRC to diffusely infiltrate the gastric wall which is seen pathologically.

In respect of contrast-enhancement, the most common type of contrast-enhancement pattern was the non-layered pattern in both carcinomas and the predominantly affected thickened layer was the high-attenuating inner layer in both carcinomas. However, the degree of contrast-enhancement was different between them. In our study, a high degree contrast-enhancement was significantly more common in AGC with SRC than that with NSRC.

It is well known that there are differences in the contrast-enhancement patterns between mature fibrosis and immature fibrosis¹⁴. Mature scar(fibrosis) is composed mainly of dense collagen fibers but few cells and vessels, whereas early or immature fibrosis contains abundant fibroblasts and neovascularity¹⁴. Subsequently, mature fibrosis shows poor contrast-enhancement, whereas early or immature fibrosis shows good contrast-enhancement. In our study, by histopathologic review, most of the SRC shows diffusely infiltrative growth of malignant cell groups intermingled with immature and mature fibrosis. Therefore, we suggest that the groups of signet ring cells intermingled with loose and immature fibrosis may induce the high degree of enhancement of SRC on CT scans. The other possible hypothesis is that signet ring cells induce more neovascularity than NSRC, and thus SRC more often shows a high degree of contrast enhancement than NSRC. Nevertheless, further evaluation with dynamic CT scan images including delayed-phase images and histopathologic correlation in a large number of patients are needed.

Although SRC and mucinous adenocarcinoma were both characterized by abundant mucin-secretion, they show somewhat different imaging features by CT scan. Gastric mucinous adenocarcinomas show the layered-enhancement pattern, composed of low-attenuated, non-enhancing mucin pools mainly in the submucosal layer and overlying strongly enhancing malignant cell groups in the mucosal layer¹². On the other hand, in SRC, diffuse infiltrative growth of malignant cell groups intermingled with loose and mature fibrosis shows the non-layered pattern with predominantly inner layer enhancement on CT scan. It is similar to non-mucinous and NSRC carcinoma.

There are several limitations to our study. We were unable to obtain arterial and delayed phase CT images in all patients, and we evaluated only the portal phase images limiting our ability to analyze dynamic changes in the enhancement pattern. Another limitation is that pathologic correlation was not done in all of the cases.

In conclusion, MDCT could not help to distinguish between AGC with SRC and that with NSRC, primarily on the basis of gross appearance, enhancement pattern and predominantly thickened layer of gastric wall. However, high degree contrast-enhancement was more common in AGC with SRC than that with NSRC. Although SRC and mucinous adenocarcinoma were both characterized by abundant mucin-secretion, SRC shows a non-layered pattern whereas mucinous adenocarcinoma shows a layered pattern on CT scan.

V. Conclusion

After the study on the differentiation of AGC with SRC and that with NSRC using multidetector CT, the conclusions are as follows.

1. MDCT could not help to distinguish between AGC with SRC and that with NSRC, primarily on the basis of gross appearance, enhancement pattern and predominantly thickened layer of gastric wall.
2. High degree contrast enhancement was more common in AGC with SRC than that with NSRC with statistical significance.
3. Most of the SRC shows diffusely infiltrative growth of malignant cell groups intermingled with immature and mature fibrosis. And, the groups of signet ring cells and immature fibrosis shows good contrast enhancement, whereas mature fibrosis shows poor enhancement.
4. We suggest that the groups of signet ring cells intermingled with loose and immature fibrosis may induce the high degree of enhancement on CT scans.

But, further evaluation with dynamic CT scan images including delayed phase images and histopathologic correlation in a large number of patients are needed.

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Abstract(in Korean)

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