Contrast-enhanced CT-gastroscopy for early gastric cancer: Imaging features and prediction of malignancy

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Early gastric cancer (EGC) is defined as a mucosal or submucosal carcinoma, regardless of lymph node status. Recent technical advances in endoscopic resection as a radical treatment for node-negative EGC have made it possible preserve gastric function and maintain the patient's quality of life.

In pathologic analysis, some types of mucosal to minute submucosal adenocarcinoma have been revealed as negative risk for lymph node metastasis and can be a target for endoscopic resection [1].

The accurate prediction of node-negative EGC is important for the determination of optimal treatment strategies in EGC patients.

However, pretreatment diagnosis based on optical endoscopy is not always accurate [2]. It is often difficult to distinguish mucosal cancer from submucosal invasive cancer definitively. It is also difficult to estimate the presence of a mixture that includes an undifferentiated component or the presence of vascular invasion, both of which are risk factors for lymph node metastasis.

In the last few decades, tumor angiogenesis has been revealed as having close correlations with tumor growth and invasion and the development of metastasis in patients with gastric cancer [3]. In pathological volumetric analyses, even EGC tended to induce tumor angiogenesis and resulting vascular invasion [4].

We therefore hypothesized that the arterial enhancement degree of EGC may be a useful alternative measure for predicting a tumor's aggressiveness.

In this study, we employed a new volume-rendering (VR) technique, the **CT gastrography wall-carving (WC) method** to demonstrate the enhancement in an arbitrary depth of the gastric wall using three-dimensional volume data sets of contrast-enhanced 64-row multi-detector CT in the arterial phase (Figure 1) [5,6].

The purpose of our study was to evaluate the relationship between arterial contrast enhancement and histologic features, with special emphasis on lymph node metastasis on contrast-enhanced CT-gastroscopy (CTG) in patients with early gastric cancer (EGC).
Images for this section:

**Volume rendering - Wall Carving method**

Digitally distended gastric lumen

Non-distended gastric lumen

**After subtraction**

Extraluminal view

Intraluminal view

Volumetric data of the gastric wall at the depth of 0 to 3 voxels from luminal surface.

The digital expansion was defined as 3 voxels (1.875 x 1.875 x 3 mm³) from the air-mucosal tissue interface of the stomach, on the basis of an estimated thickness of the normal gastric wall of about 3–4 mm.

**Fig. 1**

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Methods and Materials

Patient population

- Eighty-five patients with 93 EGCs (56 men, 29 women; age range, 26-89 years; median age, 66 years) who were examined by CTG at our institution between April 2006 and December 2010 constituted the study population (Table 1).
- Histopathologic diagnoses were obtained after gastrectomy (n = 54), endoscopic resection (n = 29), and gastrectomy after endoscopic resection (n = 2).
- Surgically treated patients were diagnosed as positive or negative for lymph node metastasis by frozen section analysis. In the endoscopically treated patients, the lymph node status of EGCs was determined by the clinical course after endoscopic resection.
- In the present study, 26 of the 29 endoscopically treated patients were defined as clinically node-negative cases. They were followed up with abdominal CT scan and/or ultrasonography for 6 to 59 months (mean, 27 months) after the endoscopic resection. No case of lymph node recurrence or distant metastasis was observed during the follow-up period.

CT protocol

- Patient preparation
  - Overnight fasted
  - In the CT room, each patient ingested 5.25 g of an effervescent agent with a small amount of water
  - Intramuscularly injected with 20 mg of butylscopolamine bromide
- CT technique
  - 64-MDCT scanner (Aquilion 64; Toshiba Medical Systems)
  - Slice thickness/collimation: 1 mm / 1 mm; a pitch of 53
  - Contrast enhancement (Iopamiron 370, Bayer Health Care)
  - 40 sec after i.v. injection of 2 mL/kg at a rate of 3 mL/sec
- Image reconstruction
  - Computer workstation equipped with dedicated software (SYNAPSE)
- Datasets at the arterial phase were converted into a virtual gastroscopy (VG), Wall-carving image (WC) and multiplanar reconstruction (MPR)

**Image analysis - Virtual gastroscopic imaging**

- Two experienced gastro-intestinal radiologists performed consensus interpretations comparing VG, WC and optical gastroscopy (OG). Although the radiologists knew the locations of the EGC to allow a lesion-by-lesion analysis, they were blinded to other clinicopathological data. The radiologists recorded whether the tumor was detectable or undetectable on VG images in the corresponding tumor location.
- The arterial contrast enhancement degree of EGCs on CT-gastroscopy using WC were determined by comparing the degrees of contrast enhancement of the surrounding healthy wall at visual interpretation. Each EGC was then classified into one of two groups according to the arterial contrast enhancement degree on WC as follows (Figure 2):

  **Group 1:** The degree of tumor enhancement was visually equal to that of the surrounding healthy wall

  **Group 2:** The degree of tumor enhancement was visually higher or lower than that of the surrounding healthy wall

  When a tumor was undetectable on both VG and WC by comparing optical gastroscopic findings, we defined the lesion as being in Group 1.

**Image analysis - MPR imaging**

**Perigastric LNs**

The presence or absence of perigastric lymph nodes (perigastric LNs) was also recorded for each patient. If visible, the short and long-axis diameters and the attenuation value of the largest perigastric LN were measured at the maximal section of the lymph node (Figure 3).

In this study, we defined "visible perigastric LN" as a perigastric LN whose short-axis diameter was greater than 3mm on MPR imaging.
We used the conventional criteria for perigastric lymph node metastasis (LNM) determined with CT for the evaluation:

Criterion 1 - LNM is present if the short-axis diameter is greater than 6mm [7].

Criterion 2 - LNM is present if the short-to-long axis ratio is greater than 0.7 and the CT attenuation value is greater than 100 HU [8].

**Clinicopathological analysis**

# Age
# Gender Male vs. Female
# Gross
- Tumor size
- Gross type*
  Depressed type #c, #, ###c,#c+#
  Flat type #b
  Elevated type #,#a, #a##c, ###c
- Location
  Upper, middle, lower
# H.E. staining
- depth of invasion
  mucosal to sm1 (sm < 500 µm) vs. sm2 (sm ≥ 500 µm)
- histological differentiation
differentiated type vs. undifferentiated type
- lymphovascular invasion (lymphatic or venous invasion)
  positive vs. negative
- ulcer formation
  presence vs. absence
- lymph node metastasis (LNM)

positive vs. negative


**Assessment and Statistical Analysis**

1. **Differences in clinicopathologic features between Group 1 and Group 2.**

Fisher's exact test, $^2$ test and Wilcoxon rank sum test was used for the comparisons of all variables between Groups 1 and 2.

2. **Comparison of diagnostic potential in multidetector CT analyses for predicting lymph node metastasis in EGCs**

a. The frequency of LNM (positive / negative; including clinically negative cases) according to the arterial enhancement degree on WC was compared by using Fisher's exact test, and the highest Odds ratio for indicating positive LNM was estimated.

b. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated when conventional criteria1 or 2 at MPR image, Group2 on WC, combined Group2 with visible perigastric LN at MPR image, combined Group2 with undifferentiated type carcinoma, were considered to be indicators of LNM.
Volume rendering - Wall Carving method -

Digitally distended gastric lumen

Non-distended gastric lumen

Extraluminal view

After subtraction

Intraluminal view

The digital expansion was defined as 3 voxels (1.875 × 1.875 × 3mm³) from the air-mucosal tissue interface of the stomach, on the basis of an estimated thickness of the normal gastric wall of about 3-4mm.

Fig. 1

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Fig. 2

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Measurement of perigastric lymph node

A short-to-long axis ratio was calculated by dividing the short-axis diameter by long-axis diameter. Region of interest (ROI) were traced free-hand inside the lymph node.

- Short-axis diameter: 6.7mm
- Long-axis diameter: 8.6mm
- Short-to-long axis ratio: 0.8 (6.7/8.6)
- CT attenuation value: 145HU

Fig. 3

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<table>
<thead>
<tr>
<th>Table 1. Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
</tr>
<tr>
<td>Gross</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Depth of invasion*</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
</tbody>
</table>

*SM1, penetration into the submucosal layer less than 500 μm
SM2, penetration into the submucosal layer ≥ 500 μm

Table 1
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Results

1. Of the 93 EGCs histopathologically evaluated from 85 patients, 59 (63%) were classified as Group 1, 34 (37%) were classified as Group 2 (Table 2).

Group 2 consisted of 15 high attenuated lesions and 19 low attenuated lesions.

**Group 1 had a higher proportion of #**

- non-depressed type lesions,
- differentiated-type adenocarcinoma,
- negative lymphovascular invasion, and
- negative ulcer findings, and the lesions in Group 1 were smaller than the Group 2 lesions (Figure 4, 5).

**Group 2 had a higher proportion of #**

- depressed type lesion,
- undifferentiated type adenocarcinoma,
- positive lymphovascular invasion,
- positive ulcer finding and
- larger than Group 1 lesion (Figure 6, 7).

2. A total of 82 patients (26 endoscopically treated patients and 56 surgically treated patients) were evaluated. Ten patients revealed positive LNM at pathologic examinations after surgery. The frequency of LNM was 12.2% of all patients (10/82). The depiction rate of visible perigastric lymph nodes (short-axis diameter larger than 3 mm) was 68% of all patients (56/82) by MPR imaging.

a. The frequency of LNM was significantly higher for Group 2 than for Group 1 (p=0.05), and more markedly so in Group 2 with undifferentiated-type adenocarcinoma (p=0.0007).

Group 2 patients with undifferentiated-type adenocarcinoma (Odds ratio, 12.9) achieved the highest Odds ratio for estimating LNM (Table 3).
b. When Group2 with undifferentiated-type adenocarcinoma was used as an indicator of positive LNM, the highest accuracy of 82.9% (68/82), sensitivity of 70.0% (7/10), specificity of 84.7% (61/82) were achieved. Two patients were diagnosed as positive LNM according to CT criteria1, whereas one patient was diagnosed as positive LNM according to CT criteria2. Conventional CT criteria for estimating LNM was high specificity(84.7-88.9%) and low sensitivity(10-20%) (Table4).
### Table 2: Differences in clinicopathologic features between Group 1 and Group 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=59)</th>
<th>Group 2 (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>67.1 ± 11.2</td>
<td>65.2 ± 11.6</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>male</td>
<td>42</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>upper</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>middle</td>
<td>33</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>lower</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Tumorsize (mm)</strong></td>
<td>22.4 ± 17.0</td>
<td>32.1 ± 19.4</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Gross</strong></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>depressed</td>
<td>40</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>non-depressed</td>
<td>19</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>differentiated type</td>
<td>45</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>undifferentiated type</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Depth of invasion</strong></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>mucosal to minute submucosal</td>
<td>43</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>(SM1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deep submucosal (SM2)</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>positive</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>55</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Accompanied ulcer finding</strong></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>presence</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>absence</td>
<td>51</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3: Univariate analysis of the predictive WC imaging feature for lymph node metastasis in early gastric cancer

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### Table 4: Comparison of diagnostic potential in multidetector CT analyses for predicting lymph node metastasis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
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<tbody>
<tr>
<td>CT criteria 1§</td>
<td>20.0</td>
<td>15.4</td>
<td>88.4</td>
<td>84.7</td>
<td>76.8</td>
</tr>
<tr>
<td>CT criteria 2#</td>
<td>10.0</td>
<td>11.1</td>
<td>87.7</td>
<td>88.9</td>
<td>79.3</td>
</tr>
<tr>
<td>Group 2</td>
<td>70.0</td>
<td>20.6</td>
<td>93.8</td>
<td>62.5</td>
<td>63.4</td>
</tr>
<tr>
<td>Group 2 with visible perigastric LN*</td>
<td>50.0</td>
<td>25.0</td>
<td>91.2</td>
<td>85.9</td>
<td>69.5</td>
</tr>
<tr>
<td>Group 2 with undifferentiated -type†</td>
<td>70.0</td>
<td>38.9</td>
<td>95.3</td>
<td>84.7</td>
<td>82.9</td>
</tr>
</tbody>
</table>

§ LNM is considered present if short-axis diameter is greater than 6mm
# LNM is considered present if short-to-long axis ratio and CT attenuation value were greater than 0.7, 100 HU, respectively
* short-axis diameter is greater than 3mm
† including undifferentiated-type or undifferentiated-type-predominant mixed type
**Fig. 4:** (a,c) Virtual (a) and optical (c) endoscopic image showing irregular mucosal change in the posterior wall of the gastric body (arrow). (b) WC imaging demonstrated the lesion as intermediate attenuation in the corresponding location. (d) Axial CT image showing small perigastric LN (short-axis dia., 5.5 mm, long-axis dia., 8 mm, attenuation value 80 HU) at the greater curvature (circle). The LN was diagnosed as negative LNM by both Criteria 1 and 2.

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Fig. 5: CT gastroscopic image (a) and optical endoscopic image (b) showing irregular mucosal change in the posterior wall of the antrum (arrows). (c) WC imaging demonstrated the lesion as intermediate enhancement area in the corresponding location. (d) Axial CT image showing oval perigastric LN (short-axis dia., 6.8 mm, long-axis dia. 8.6 mm, attenuation value 145 HU) at the greater curvature (circle). The LN was diagnosed as positive LNM by both Criteria 1 and 2.

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Fig. 6: a) Optical endoscopic image showing a shallow depressed lesion that is pale or discolored compared with the normal non-cancerous mucosa on the greater curvature of the gastric body (white arrows). WC image (b) and MPR image (c) demonstrate that the degree of contrast enhancement of the lesion was lower than that of surrounding healthy wall (white arrow). (d) Axial CT image showing oval perigastric LN (short-axis dia., 4.6 mm, long-axis dia., 5 mm, attenuation value 111 HU) at the greater curvature (circle). The LN was diagnosed as positive LNM by Criterion 2.

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Fig. 7: Optical endoscopic image (a) and CT gastroscopic image (b) showing irregular ulcerative lesion in the posterior wall of the gastric angle (arrows). (c) WC imaging demonstrated the lesion as a marked enhancement area in the corresponding location. (d) Axial CT image showing oval perigastric LN (short-axis dia., 4.2 mm, long-axis dia. 6.7 mm, attenuation value 93.8 HU) at the greater curvature (circle). The LN was diagnosed as negative LNM by both Criteria 1 and 2.

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Conclusion

#The incidence of LNM for Group 2 (higher or lower than normal wall) on WC was higher than that for Group 1 (equal to normal wall) on WC.

Group 2 consisted of high- and low-attenuated lesions.

The high-attenuated lesions included deep submucosal invasive cancer (80%, 12/15), positive lymphovascular invasion (45%, 7/15), and positive ulcer formation (60%, 6/15), whereas the low-attenuated lesions included undifferentiated type carcinoma (63%, 12/19) and positive ulcer formation (47%, 9/19).

#These pathologic features are high-risk factors for LNM

# The extent of arterial contrast enhancement may vary according to the tumor size and histologic differentiation, lymphovascular invasion, and ulcer formation.

- Histology:
  differentiated carcinoma; normovascular # hypervascular [4]
  undifferentiated carcinoma; hypovascular [4]
- Ulcer formation: healing ulcer induced angiogenesis [12]

# WC imaging may be of help in the differentiation between node-negative EGC and node-positive EGG in a different way from the current morphologic diagnosis for EGCs.

- The diagnostic performance of endoscopy is low accuracy for the prediction of submucosal invasive cancer (44% to 66%) [2].
- The sensitivity of conventional CT criteria for positive LNM in EGC is extremely low (17% to 27%) [10].

Conclusions

# The degree of arterial contrast enhancement on wall-carving imaging correlated with histologic differentiation, lymphovascular invasion and ulcer formation.
This VR display may provide additional information for making the diagnosis of lymph node metastasis in patients with early gastric cancer.
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