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Original Article

Correlation between White Globe Appearance and Clinicopathologic Characteristics in Early Gastric Cancer

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Background/Aims: Magnifying endoscopy with narrow-band imaging (ME-NBI) enables the visualization of detailed microsurface (MS) and microvascular (MV) structures in the gastrointestinal tract. White globe appearance (WGA) is a small whitish lesion with a globular shape identified during ME-NBI for early gastric cancer (EGC). This study aimed to investigate the associations between WGA, clinicopathological characteristics, and other ME-NBI findings in patients with EGC.

Methods: The presence or absence of WGA in 122 patients (126 lesions) with an endoscopic diagnosis of EGC who underwent ME-NBI before endoscopic or surgical resection was prospectively collected and retrospectively analyzed. During ME-NBI, the MS and MV patterns and the presence of WGA and white opaque substances (WOS) were investigated. EGC cases were categorized as differentiated or undifferentiated type, and mucosal, submucosal, or advanced.

Results: Of 126 lesions, WGA was observed in 25 (19.8%). WGA was associated with tumor size (≤2 cm [17/63, 27.0%] vs >2 cm [8/63, 12.7%]; p=0.044), histologic type (differentiated type [22/89, 24.7%] vs undifferentiated type [3/37. 8.1%]; p=0.033), and tumor location (upper third [1/11, 9.1%] vs middle third [18/58, 31.0%] and lower third [6/57, 10.5%]; p=0.017). Although WGA was observed more frequently in lesions with an oval/tubular MS pattern, a fine-network MV pattern, and the absence of WOS, the difference was not statistically significant (MS pattern, p=0.358; MV pattern, p=0.212; WOS, p=0.121, respectively).

Conclusions: WGA was associated with small tumor size, differentiated-type histology, and middle-third tumor location, and was more frequently observed in lesions with an oval/tubular MS and fine-network MV patterns and the absence of WOS. **(Gut Liver 2025;19:50-58)**

Key Words: Magnifying endoscopy; Narrow band imaging; Stomach neoplasms; White globe appearance

INTRODUCTION

Magnifying endoscopy with narrow-band imaging (ME-NBI) enables clear visualization of the microsurface (MS) architecture and microvascular (MV) structures on the gastric mucosa. Since the vessel plus surface classification system for diagnosing early gastric cancer (EGC) was first suggested by Yao *et al.*,[1] the clinical usefulness of ME-NBI in the diagnosis and characterization of EGC has been reported.[2-8] In our previous study, differentiated-type EGC mainly showed an oval and/or tubular MS pattern and a fine network or loop MV pattern, while undifferentiated-type EGC mainly showed absent MS and corkscrew MV patterns.[2]

White globe appearance (WGA) is reported as an endoscopic marker for gastric cancer observed during ME-NBI.[9] WGA is defined as a small whitish structure with a globular shape located underneath the gastric epithelium. It is histopathologically associated with intraglandular necrotic debris (reported as a histopathological marker

specific for gastric cancer), seen as eosinophilic material with necrotic epithelial fragments inside the dilated gland lumen.[9,10] WGA is reported to have a high specificity in differentiating EGC from non-cancerous lesions including low-grade adenoma[9,10] and a high interobserver concordant rate.[10,11]

In addition to the diagnostic usefulness of WGA, there have been few studies on the clinical significance of WGA in EGC, especially on the association of WGA with MS and MV patterns on ME-NBI. Therefore, this study aimed to investigate the associations between WGA, clinicopathological characteristics, and other ME-NBI findings in patients with EGC.

MATERIALS AND METHODS

1. Patients

Between October 2018 and March 2020, 135 patients (with 139 lesions) with an endoscopic diagnosis of EGC underwent ME-NBI. Of these patients, 13 were excluded from our study because of the lack of final histologic results owing to loss to follow-up. Thus, 126 EGC lesions from 122 patients (86 men and 36 women; age range, 37 to 87 years; median age, 66 years) were included in this study (Fig. 1). ME-NBI data were prospectively collected and retrospectively analyzed, with special focus on MS and MV patterns, and the presence or absence of white opaque substances (WOS) and WGA in each lesion. The study protocol was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (IRB number: 2401-002-134). The requirement for acquisition of informed consent from patients was waived by the IRB owing to the retrospective nature of this study.

2. ME-NBI

The EVIS-LUCERA SPECTRUM system (CV-260, CV-290; Olympus, Tokyo, Japan) and high-resolution magnifying endoscopes (GIF-H260Z, GIF-H290Z; Olympus) were used for video endoscopy. To obtain a clear view during ME-NBI, a soft black hood (MB-46; Olympus) was attached to the distal tip of the endoscope to maintain a proper focus distance. A single experienced endoscopist (G.H.K.) performed ME-NBI, and all endoscopies were performed under conscious sedation with 2–5 mg midazolam. After routine observation, ME-NBI examination of the EGC was performed to evaluate MS and MV patterns. MS patterns were classified as (1) oval and/or tubular, (2) papillary, (3) destructive, or (4) absent, while MV patterns were classified as (1) loop, (2) fine network, or (3) corkscrew, based on our previous study (Fig. 2).[2] If lesions showed combined MS or MV patterns, the predominant pattern was used for classification. WOS was defined as a white substance that was present in the superficial layer of the mucosa, obscuring subepithelial MV structures, and was clearly visualized on ME-NBI.[12] When WOS was observed in more than 10% of the lesion area, the lesion was determined to be WOS (+). WGA was defined based on two features identified during ME-NBI: (1) a small, <1 mm, whitish structure with a globular shape and (2) the presence of overlying microvessels on the lesion (Fig. 3).[9] Lesions with these findings were determined to be WGA (+).

The location (upper third, middle third, or lower third), color (isochromatic, reddish, or discolored), and macroscopic shape (flat, elevated, or depressed) were evaluated during endoscopy. The color of the lesions was compared with surrounding non-cancerous mucosa and classified as isochromatic (same as the surrounding mucosa), reddish, or discolored.[13] The macroscopic shapes of the lesions were classified based on the Japanese Classification of Gastric Carcinoma:[14] type I (protruding), type II (non-protruding and non-excavated), or type III (excavated). Type II lesions were sub-classified as slightly elevated (IIa), flat (IIb), or slightly depressed (IIc). All lesions were classified into three groups: elevated (I, IIa), flat (IIb), and depressed (IIc, III).

The endoscopic grade of atrophic gastritis was assessed

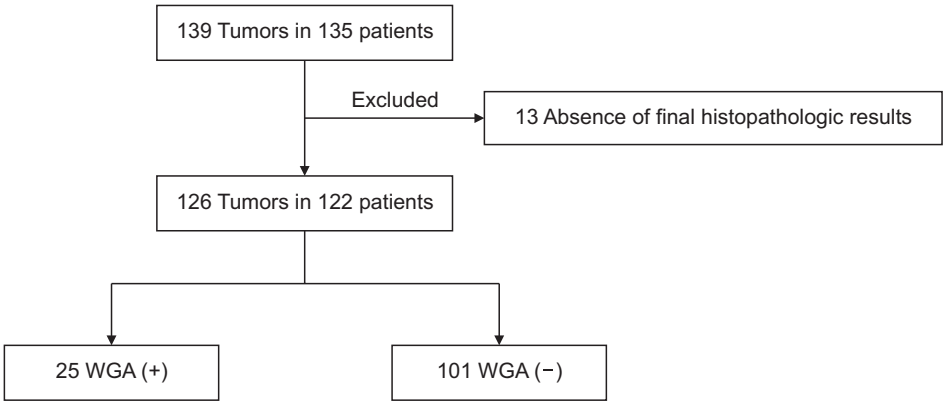

Fig. 1. Flowchart showing patient inclusion in the study. WGA, white globe appearance.

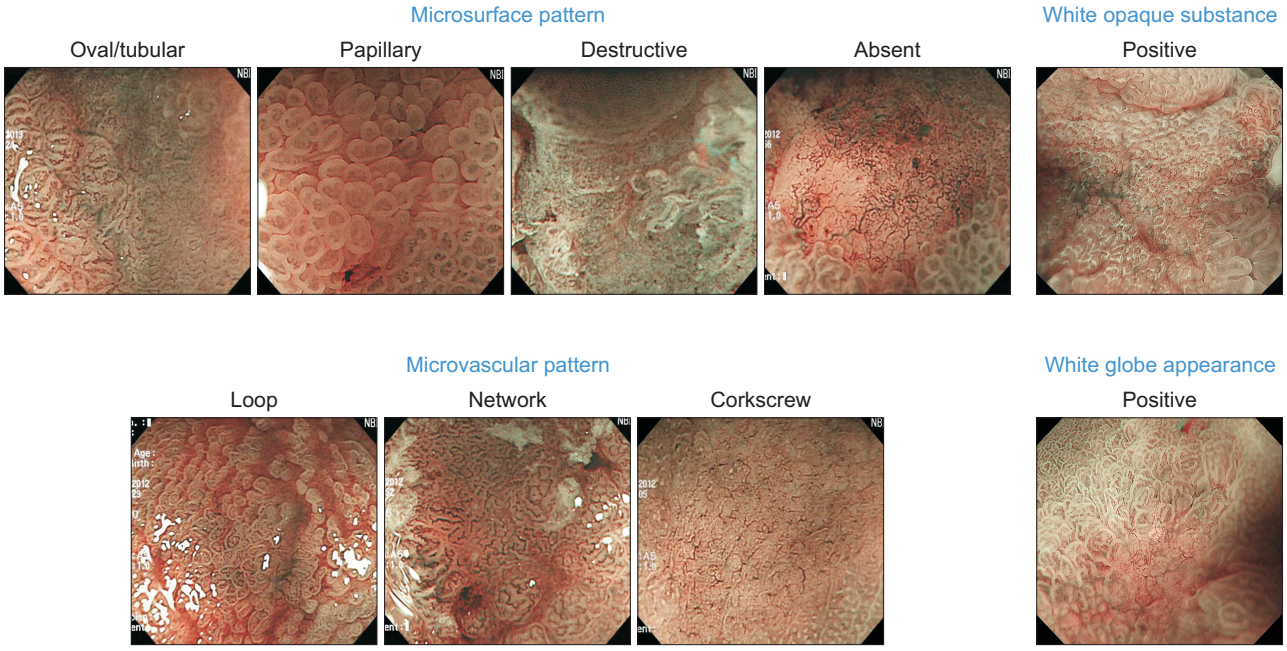

Fig. 2. Classification of microsurface and microvascular patterns, white opaque substance, and white globe appearance using magnifying endoscopy with narrow-band imaging in early gastric cancer. Adapted from the article of Ok *et al.* Gut Liver 2016;10:532-541.[2]

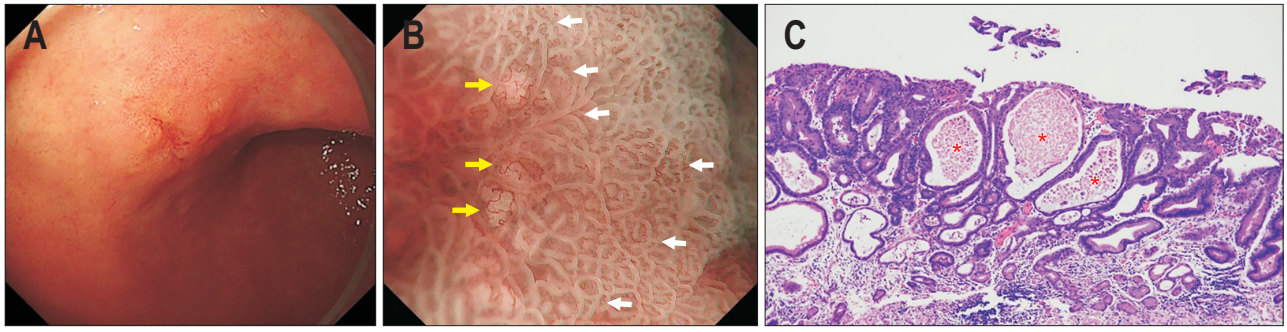

Fig. 3. A representative case of early gastric cancer having a white globe appearance (WGA) in magnifying endoscopy with narrow-band imaging (ME-NBI). (A) A 1.2-cm sized, isochromatic, slightly depressed lesion is seen at the anterior wall of the gastric lower body. (B) On ME-NBI, the lesion reveals an oval and/or tubular microsurface pattern and a loop microvascular pattern. White opaque substance is not seen. Three WGAs (yellow arrows) are observed at the inner side of cancerous mucosa close to the demarcation line between the cancerous mucosa and the surrounding mucosa (white arrows). The typical features of WGA are a whitish lesion with a globular shape and the presence of overlying microvessels. (C) The final histopathology is a well-differentiated adenocarcinoma, limited to the lamina propria. Intraglandular necrotic debris (red asterisks) is present within markedly dilated neoplastic glands underneath the gastric neoplastic epithelium (hematoxylin and eosin stain, ×100).

using the Kimura-Takemoto classification.[15] In the closed type, the atrophic border remained on the lesser curvature of the stomach, whereas in the open type, the atrophic border no longer existed on the lesser curvature but extended along the anterior and posterior walls of the stomach. *Helicobacter pylori* infection status was evaluated using the rapid urease test, histology, and the ^{13}C urea breath test. If any of the tests yielded a positive result, *H. pylori* infection was considered present.

3. Histologic assessment

Endoscopic submucosal dissection (ESD) or gastrectomy was undergone within 2 weeks of ME-NBI. The resected specimens were fixed in 10% buffered formalin. Carcinoma and adjacent non-neoplastic mucosa were serially cut into 2-mm slices for ESD specimens and 5-mm slices for surgical specimens, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for histologic examination. The tumor size, depth of invasion, degree of differentiation, and presence of ulceration were assessed microscopically based on the Japanese Classifica-

tion of Gastric Carcinomas.[14]

4. Statistical analyses

Variables are expressed as medians, ranges, and proportions. Differences in the clinicopathological characteristics and other ME-NBI findings according to the presence or absence of WGA were evaluated using the chi-square test, Fisher exact test, or independent t-test. Differences in ME-NBI findings according to the histologic type or invasion depth were evaluated using the chi-square test or Fisher exact test. Statistical calculations were performed using SPSS version 27.0 software for Windows (IBM Corp., Armonk, NY, USA). Results were considered statistically significant when the p-value was <0.05.

RESULTS

1. Baseline clinicopathological characteristics of patients with EGC

Of the 126 EGC lesions examined in this study, 11, 58, and 57 were located in the upper, middle, and lower thirds of the stomach, respectively (Table 1). The most common macroscopic shape was the depressed shape (92/126,

Table 1. Clinicopathological Characteristics of Early Gastric Cancers According to the Presence or Absence of WGA during Magnifying Endoscopy with Narrow-Band Imaging

Characteristic	Total (n=126)	WGA (+) (n=25)	WGA (–) (n=101)	p-value
Sex*				0.364
Male	86 (68.3)	18 (78.3)	68 (68.7)	
Female	36 (28.6)	5 (21.7)	31 (31.3)	
Age, yr	65.3±11.0	63.3±11.7	65.7±10.9	0.343
Location				0.017
Upper third	11 (8.7)	1 (4.0)	10 (9.9)	
Middle third	58 (46.0)	18 (72.0)	40 (39.6)	
Lower third	57 (45.2)	6 (24.0)	51 (50.5)	
Tumor color				0.294
Normal	76 (60.3)	12 (48.0)	64 (63.4)	
Reddish	39 (31.0)	11 (44.0)	28 (27.7)	
Discolored	11 (8.7)	2 (8.0)	9 (8.9)	
Macroscopic shape				0.926
Elevated	26 (20.6)	6 (24.0)	20 (19.8)	
Flat	8 (6.3)	1 (4.0)	7 (6.9)	
Depressed	92 (73.0)	18 (72.0)	74 (73.3)	
Ulceration				0.253
Absent	114 (90.5)	21 (84.0)	93 (92.1)	
Present	12 (9.5)	4 (16.0)	8 (7.9)	
Tumor size, cm	2.6±1.6	2.1±1.5	2.7±1.6	0.148
Tumor size				0.044
≤2 cm	63 (50.0)	17 (68.0)	46 (45.5)	
>2 cm	63 (50.0)	8 (32.0)	55 (54.5)	
H. pylori infection				0.966
Absent	66 (52.4)	13 (52.0)	53 (52.5)	
Present	60 (47.6)	12 (48.0)	48 (47.5)	
Atrophic gastritis				0.562
C-type	22 (17.4)	3 (12.0)	19 (18.8)	
O-type	104 (82.6)	22 (88.0)	82 (81.2)	
Histologic type				0.033
Differentiated type	89 (70.6)	22 (88.0)	67 (66.3)	
Undifferentiated type	37 (29.4)	3 (12.0)	34 (33.7)	
Tumor depth				0.584
Mucosa	96 (76.2)	21 (84.0)	75 (74.3)	
Submucosa	26 (20.6)	4 (16.0)	22 (21.8)	
Subserosa	4 (0.3)	0	4 (4.0)	
Treatment method				0.094
Endoscopic resection	72 (57.1)	18 (72.0)	54 (53.5)	
Surgical resection	54 (42.9)	7 (28.0)	47 (46.5)	

Data are presented as number (%) or mean±SD.
WGA, white globe appearance; *H. pylori, Helicobacter pylori.*
*Two patients had two lesions, and one had three lesions.

73.0%). The mean tumor size was 2.6 cm (range, 0.4 to 8.3 cm). Seventy-two lesions were treated with ESD, and 54 were treated surgically. The final histologic assessment results with regard to invasion depth and histologic type were as follows: 96 lesions were mucosal cancers, 26 were submucosal cancers, and four were advanced cancers, and 89 lesions were differentiated types and 37 were undifferentiated types.

2. Association between WGA and clinicopathologic characteristics

The prevalence of WGA in EGC lesions was 19.8% (25/126), and the mean number of WGA in the 25 WGA (+) lesions was 2 (range, 1 to 7). Almost all WGAs were observed at the inner side of cancerous mucosa close to the demarcation line between the cancerous mucosa and the surrounding mucosa (Fig. 3). WGA was more frequently observed in lesions with a small size (≤2 cm [27.0%, 17/63] vs >2 cm [12.7%, 8/63], p=0.044) and differentiated-type histology (differentiated type [24.7%, 22/89] vs undifferentiated type [8.1%, 3/37], p=0.033) (Table 1). WGA was more frequently observed in the middle third of the stomach than in the upper and lower thirds (31.0% [18/58] vs 9.1% [1/11] and 10.5% [6/57], respectively, p=0.017). There was no correlation between the presence of WGA and sex, age, tumor color, macroscopic type, ulceration, *H. pylori* infection status, the grade of atrophic gastritis, or tumor depth (all p>0.05).

3. ME-NBI findings of EGC according to histologic type

First, MS patterns were analyzed according to histologic type. Among the 89 differentiated-type cancers, an oval and/or tubular pattern was observed in 75 (84.3%), a destructive pattern in nine (10.1%), a papillary pattern in four (4.5%), and an absent pattern in one (1.1%) (Table 2). Among the 37 undifferentiated-type cancers, an absent MV pattern was observed in 17 (45.9%), an oval and/or tubular pattern in 14 (37.8%), a papillary pattern in four (10.8%), and a destructive pattern in two (5.4%). Accordingly, the main MS pattern was oval and/or tubular in differentiated-type cancers and absent in undifferentiated-type cancers (p<0.001). In addition, MV patterns were analyzed according to histologic type. Among the 89 differentiated-type cancers, a fine network pattern was observed in 45 (50.6%), a loop pattern in 42 (47.2%), and a corkscrew pattern in two (2.2%) (Table 2). Among the 37 undifferentiated-type cancers, a corkscrew pattern was observed in 26 (70.3%), a fine network pattern in six (16.2%), and a loop pattern in five (13.5%). Accordingly, the main MV pattern was fine network or loop in differentiated-type cancers and corkscrew in undifferentiated-type cancers (p<0.001). WOS was more frequently observed in differentiated-type cancers than in undifferentiated-type cancers; however, this difference was not significant (16.9% [15/89] vs 8.1% [3/37], p=0.201).

4. ME-NBI findings of EGC according to the invasion depth

The main MS pattern in mucosal cancers was oval and/or tubular (77/96, 80.2%) (Table 3). Although an oval and/or tubular MS pattern was predominant in submucosal or deeper cancers (12/30, 40.0%), destructive and absent MS patterns were also frequently observed (30.0% and 26.7%, respectively). There was a significant difference in the MS patterns between mucosal cancers and submucosal or deeper cancers (p<0.001). A loop MV pattern was more frequently observed in mucosal cancers (42/96, 43.8%),

Table 2. Magnifying Endoscopy with Narrow-Band Imaging of Early Gastric Cancers According to the Histologic Type of the Tumor

Variable	Differentiated type (n=89)	Undifferentiated type (n=37)	p-value
Microsurface pattern			<0.001
Oval and/or tubular	75 (84.3)	14 (37.8)	
Papillary	4 (4.5)	4 (10.8)	
Destructive	9 (10.1)	2 (5.4)	
Absent	1 (1.1)	17 (45.9)	
Microvascular pattern			<0.001
Loop	42 (47.2)	5 (13.5)	
Fine network	45 (50.6)	6 (16.2)	
Corkscrew	2 (2.2)	26 (70.3)	
White opaque substance			0.201
Present	15 (16.9)	3 (8.1)	
Absent	74 (83.1)	34 (91.9)	
White globe appearance			0.033
Present	22 (24.7)	3 (8.1)	
Absent	67 (75.3)	34 (91.9)	

Data are presented as number (%).

Table 3. Magnifying Endoscopy with Narrow-Band Imaging of Early Gastric Cancers According to the Invasion Depth of the Tumor

Variable	Mucosal cancer (n=96)	Submucosal or deeper cancer (n=30)	p-value
Microsurface pattern			<0.001
Oval and/or tubular	77 (80.2)	12 (40.0)	
Papillary	7 (7.3)	1 (3.3)	
Destructive	2 (2.1)	9 (30.0)	
Absent	10 (10.4)	8 (26.7)	
Microvascular pattern			0.006
Loop	42 (43.8)	5 (16.7)	
Fine network	38 (39.6)	13 (43.3)	
Corkscrew	16 (16.7)	12 (40.0)	
White opaque substance			0.560
Present	15 (15.6)	3 (10.0)	
Absent	81 (84.4)	27 (90.0)	
White globe appearance			0.306
Present	21 (21.9)	4 (13.3)	
Absent	75 (78.1)	26 (86.7)	

Data are presented as number (%).

Table 4. Association Between WGA and Other Findings on Magnifying Endoscopy with Narrow-Band Imaging of Early Gastric Cancers

Variable	WGA (+) (n=25)	WGA (–) (n=101)	p-value
Microsurface pattern			0.358
Oval and/or tubular	21 (84.0)	68 (67.3)	
Papillary	1 (4.0)	7 (6.9)	
Destructive	2 (8.0)	9 (8.9)	
Absent	1 (4.0)	17 (16.8)	
Microvascular pattern			0.212
Loop	6 (24.0)	41 (40.6)	
Fine network	14 (56.0)	37 (36.6)	
Corkscrew	5 (20.0)	23 (22.8)	
White opaque substance			0.121
Present	1 (4.0)	17 (16.8)	
Absent	24 (96.0)	84 (83.2)	

Data are presented as number (%).
WGA, white globe appearance.

and a corkscrew MV pattern was more frequently observed in submucosal or deeper cancers (12/30, 40.0%). There was a significant difference in the MV pattern between mucosal cancers and submucosal or deeper cancers (p=0.006). No significant differences were observed in the presence of WOS and WGA between mucosal cancers and submucosal or deeper cancers (15.6% [15/96] vs 10.0% [3/30], p=0.560 and 21.9% [21/96] vs 13.3% [4/30], p=0.306, respectively).

5. Association between WGA and other ME-NBI findings

Among the 25 WGA (+) lesions, an oval and/or tubular pattern was observed in 21 (84.0%), a destructive pattern in two (8.0%), a papillary pattern in one (4.0%), and an absent pattern in one (4.0%) (Table 4). Among the 101 WGA (–) lesions, an oval and/or tubular pattern was observed in 68 (67.3%), an absent MV pattern in 17 (16.8%), a destructive pattern in nine (8.9%), and a papillary pattern in seven (6.9%). Although WGA was more frequently observed in lesions with an oval and/or tubular MS pattern than in those with other MS patterns, there was no significant difference between WGA and MS patterns (p=0.358). In terms of MV patterns, a loop MV, fine network, and corkscrew patterns were observed in six (24.0%), 14 (56.0%), and five (20.0%) WGA (+) lesions, and 41 (40.6%), 37 (36.6%), and 23 (22.8%) WGA (–) lesions, respectively; there was no significant difference between WGA and MV patterns (p=0.212). WGA was more frequently observed in WOS (–) lesions than in WOS (+) lesions; however, the difference was not statistically significant (p=0.121).

DISCUSSION

In the present study, we examined the presence or absence of WGA in ME-NBI and investigated the clinicopathological significance of WGA in EGC. WGA was observed in 19.8% of EGC lesions and its presence was associated with small tumor size (≤2 cm), differentiated-type histology, and location in the middle third of the stomach. Compared with other ME-NBI findings, WGA was not associated with MS and MV patterns, or WOS. To the best of our knowledge, this is the first report on an association between WGA and other ME-NBI findings.

WGA is known to correspond to the endoscopic visualization of the apoptotic-necrotic phenomenon[9] and it histopathologically represents the intraglandular necrotic debris, which is seen as eosinophilic material with necrotic epithelial fragments within the dilated gland lumen. The sensitivity and specificity of intraglandular necrotic debris for gastric cancer have been reported to be 43.1% and

98.7%, respectively,[16] and those of WGA for differentiating gastric cancer from other lesions and low-grade adenoma were 21.4% and 97.5%,[10] and 21.5% and 100%, respectively.[9] The low sensitivity of WGA for diagnosing gastric cancer compared to intraglandular necrotic debris can be explained by the fact that only intraglandular necrotic debris located just beneath the gastric epithelium can be detected as WGA during ME-NBI. However, despite its low sensitivity, its high specificity suggests that WGA is a valuable endoscopic marker of gastric cancer. In the present study, the prevalence of WGA in EGC was 19.8%, similar to the results of previous studies (21% to 26%).[9,11,17]

The presence of WGA indicates the presence of a glandular structure in the lesion. Therefore, WGA (+) EGC includes components of differentiated-type histology, such as well-to-moderately differentiated tubular adenocarcinoma.[17] In the present study, the differentiated-type histology was associated with the presence of WGA. In contrast, two previous studies reported no correlation between WGA and histologic type.[9,18] However, the number of undifferentiated-type EGC included in these studies was only four and 13 lesions, respectively. In addition, in a study that evaluated intraglandular necrotic debris in gastric biopsy and surgical specimens, intraglandular necrotic debris was mainly observed in differentiated-type EGC.[16] These results support the higher incidence of WGA in differentiated-type EGC than in undifferentiated-type EGC observed in the present study.

In the present study, WGA was more frequently observed in small-sized tumors (≤2 cm), which is consistent with the result of a previous study which reported that the size of WGA (–) EGC was significantly larger than that of WGA (+) EGC.[10] As the tumor size increases, the missing rate for detecting WGA also could increase. However, unlike previous studies, we prospectively collected ME-NBI findings for each lesion; therefore, we could have overcome this limitation. We believe that a higher incidence of WGA in small-sized EGC would be helpful for the correct diagnosis of cancer in small lesions. Further prospective studies on the usefulness of WGA for diagnosing cancer in small gastric lesions are required to validate our results.

WGA was also more frequently observed in the middle third of the stomach than in the upper and lower thirds of the stomach, similar to the result of a recent study that WGA (+) EGCs were mainly located in the middle third of the stomach (62%).[17] Contrarily, there was no correlation between WGA and invasion depth as observed in previous studies.[9,18] Although Watanabe *et al.*[16] previously reported that submucosal cancers showed the highest incidence of intraglandular necrotic debris, they included intramucosal or submucosal cancers with microinvasion into the submucosa because they recruited patients who were candidates for ESD. In addition, as mentioned above, ME-NBI can recognize only intraglandular necrotic debris located just beneath the gastric epithelium as WGA. Therefore, further studies evaluating the presence of WGA according to the location of intraglandular necrotic debris in histopathological specimens are needed. Furthermore, there was no correlation between WGA and tumor color, macroscopic shape, ulceration, *H. pylori* infection, or the grade of atrophic gastritis in the present study.

Several studies have reported differences in MS and MV patterns according to the histologic type and invasion depth of EGC. In the present study, the main MS patterns in differentiated-type and undifferentiated-type cancers were an oval and/or tubular pattern and an absent pattern, respectively, whereas the main MV patterns in differentiated-type and undifferentiated-type cancers were fine network and loop patterns and a corkscrew pattern, respectively. In terms of invasion depth, while an oval and/or tubular MS pattern and a loop MV pattern were predominant in mucosal cancers, the proportion of destructive and absent MS patterns and a corkscrew MS pattern was higher in submucosal or deeper cancers. These results are consistent with those of our previous study[2] and other studies.[19-22] The histopathological basis for the difference in MS and MV patterns according to histologic type and invasion depth can be explained as follows. Histopathologically, proliferation of vessels within the neoplastic interstitial tissue is usually observed in the differentiated-type cancers, whereas destruction of vascular architecture in the normal mucosa by infiltrating cancer cells in the absence of proliferation in the interstitial tissue is observed in the undifferentiated-type cancers.[23,24] These differences contribute to make differences in MS and MV patterns between the two histologic types; differentiated-type cancers display maintenance of gland structures (an oval and/or tubular MS pattern) with abundant vasculature (loop and fine network MV patterns), whereas undifferentiated-type cancers typically display poor vasculature (a corkscrew MV pattern). In addition, an absent MS pattern in undifferentiated-type cancers is caused by neoplastic cell infiltration destroying the glandular architecture.[25] Also, the deeply invasive portion of differentiated-type cancers tends to be de-differentiated than the surrounding areas and exhibits desmoplastic reactions, and the glandular portion of the tumor is less dense.[2] These histopathological changes could explain the predominance of the destructive MS pattern and corkscrew MV pattern in submucosal cancers.

WOS is frequently observed in gastric epithelial neoplasms (adenoma or cancer) with an intestinal phenotype.[26] WOS can be seen as white substances observed

through the reflection or strong scattering of the projected light from the endoscope on minute lipid droplets accumulated in and under the epithelium.[27,28] It has been reported that WOS (+) tumors have an intestinal mucin phenotype (intestinal or gastrointestinal phenotype)[27] and that WOS can be an indicator of differentiated-type cancers because WOS is not observed in undifferentiated-type cancers.[29] In the present study, WOS was also more frequently observed in differentiated-type cancers than in undifferentiated-type cancers.

Because WGA is more frequently observed in differentiated-type cancers, we investigated the association between WGA and other ME-NBI findings. Although WGA was more frequently observed in lesions with oval and/or tubular MS and fine network MS patterns, there was no significant difference in WGA according to MS and MV patterns. Furthermore, no association was observed between WGA and WOS. WGA was observed in only one of the 18 WOS (+) lesions. This could be partially explained by the fact that when WOS is present, the projected light cannot reach the subepithelial area, resulting in poor visibility of the intraglandular necrotic debris located underneath the epithelium.

Our study has several limitations to be addressed. First, because we performed ME-NBI after gastric cancer was confirmed histopathologically via endoscopic forceps biopsy, the ME-NBI findings, such as MV and MS patterns, might have been influenced by the biopsy. Second, because gastric cancers are classified into differentiated or undifferentiated types based on the predominant histologic type of the tumor, the MS and MV patterns observed in this study might not exactly indicate the corresponding histology.[2] However, we included a relatively large number of lesions and categorized ME-NBI findings based on the predominant pattern of the tumor, thereby overcoming this limitation to some degree. Third, we did not investigate the presence or absence of intraglandular necrotic debris in the histopathological specimens. According to a previous study, discrepancies in visualization of WGA and its association with histological intraglandular necrotic debris were present, because ME-NBI and ESD or surgery were usually performed on different days.[9] Lastly, since ME-NBI was performed by a single experienced endoscopist, interobserver variation was not evaluated. Although ME-NBI findings, especially WGA, are thought to be reliable according to recent reports,[11,21,30,31] interobserver variability in the assessment of ME-NBI findings must be evaluated before clinical application.

In conclusion, WGA was associated with small tumor size, differentiated-type histology, and middle-third tumor location, and was more frequently observed in lesions with an oval/tubular MS and fine-network MV patterns and the absence of WOS. Therefore, WGA may be helpful in the characterization of EGC during ME-NBI.

CONFLICTS OF INTEREST

G.H.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: G.H.K. Data acquisition: G.H.K., K.K., H.K.J., D.C.J., M.W.L., B.E.L. Data analysis and interpretation: D.J.J., G.H.K., K.K. Drafting of the manuscript: D.J.J., G.H.K. Approval of final manuscript: all authors.

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