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Usefulness of Magnifying Endoscopy with Narrow-Band Imaging for Diagnosing Mixed Poorly Differentiated Gastric Cancers

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Keywords
Biopsy · Gastric cancer · Narrow-band imaging · Undifferentiated-type carcinoma · Poorly differentiated adenocarcinoma

Abstract
Introduction: Curative rates of endoscopic treatment for undifferentiated-type early gastric cancer (EGC), particularly mixed poorly differentiated adenocarcinoma (MIXED-POR), are lower than those of endoscopic treatment for the differentiated type. Magnifying endoscopy with narrow-band imaging (ME-NBI) is useful for diagnoses of the histological type. This study aimed to investigate the detection rates of MIXED-POR among undifferentiated-type EGCs using biopsy and ME-NBI in order to improve curative rates through endoscopic treatment. ***Methods:*** We analyzed 267 lesions initially subjected to endoscopic submucosal resection (ESD) and histologically diagnosed as undifferentiated-type EGCs between July 2005 and December 2016 at our hospital. We obtained written informed consent from all participants. Biopsy and ME-NBI findings were compared to distinguish pure signet ring cell carcinoma (PURE-SIG) and MIXED-POR. ME-NBI findings were divided into 2 categories depending on the presence of irregular vessels. Results of biopsy and ME-NBI (combination method) were also analyzed, and detection rates of MIXED-POR and PURE-SIG were evaluated in terms of sensitivity, specificity, and accuracy. ***Results:*** Overall, 114 lesions were analyzed. Fifty-eight lesions (50.9%) were identified as MIXED-POR. With biopsy, the detection rate of MIXED-POR was significantly lower than that of PURE-SIG ($p < 0.0001$). ME-NBI detected significantly more MIXED-POR with irregular vessels than PURE-SIG ($p < 0.0001$). The combination method could detect significantly more MIXED-POR than PURE-SIG ($p < 0.0001$). The sensitivity and accuracy for MIXED-POR diagnosis were significantly higher with the combination method than with biopsy alone ($p < 0.0001$). ***Discussion/Conclusion:*** Combining biopsy and ME-NBI improved the accuracy of pretreatment diagnosis before ESD in undifferentiated-type cancer.

Introduction

Endoscopic submucosal resection (ESD) is a common treatment for early gastric cancer (EGC) that is statistically unlikely to result in lymph node metastasis during treatment [1, 2]. Although the standard treatment for undifferentiated-type EGCs is surgery, they may also be treated as an expanded indication of ESD in cases of "T1a, 2 cm or smaller, and without ulceration," because the

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lymph node metastasis rate is ≤1% according to the Japanese Gastric Cancer Treatment Guidelines 2018 (ver. 5) [3]. However, the incidence of undifferentiated-type EGC lesions that do not require additional therapy, called endoscopy curability B (eCura B), is 63.9–82.4%, which is lower than the 94.0% rate of differentiated adenocarcinoma lesions that do not require additional therapy, called endoscopy curability A (eCura A) [4–11]. This indicates that the diagnosis of indications of ESD is more difficult in undifferentiated-type than in differentiated-type EGCs. We previously reported that ESD treatment results were poorer and the diagnosis of ESD indications was more difficult in mixed poorly differentiated adenocarcinoma (MIXED-POR: por > sig, sig > por, por) than in pure signet ring cell carcinoma (PURE-SIG) [12]. If MIXED-POR is detected before ESD, a more careful diagnosis is enabled, and the rate of eCura B may improve. In general, the histological type is diagnosed by biopsy before ESD [13], but the reported accuracy of detection by biopsy is 80–90%, and some cases are misdiagnosed [14, 15]. Magnifying endoscopy with narrow-band imaging (ME-NBI) is reportedly useful for diagnosing the histological type [16–19]. We have previously reported that the combination of biopsy and ME-NBI has a positive effect on the biopsy to distinguish between differentiated-type and undifferentiated-type EGCs [20]. However, the efficacy of the combination of pretreatment biopsy and ME-NBI in undifferentiated-type EGC has not yet been reported. If this combination method is effective, it becomes possible to make a more careful diagnosis before initiating treatment, and, as a result, the rate of eCura B may improve. Therefore, this study aimed at investigating the detection rates of MIXED-POR by biopsy and ME-NBI individually as well as any additional advantages of combining both methods in undifferentiated-type EGCs.

Materials and Methods

Informed Consent

After providing detailed explanations to patients and their parents/guardians of the methods and risks of ESD as an expanded indication, we obtained written informed consent from all participants. All patients agreed to the use, in our study, of the results obtained from the treatment.

Research Involving Human Participants and/or Animals

This study was approved by the Institutional Review Board (IRB) of Cancer Institute Hospital (IRB No. 2017-1033). This study was conducted in compliance with the principles of the Declaration of Helsinki issued in 1964 and revised thereafter. Before recording the data, all personal identification information was removed.

Subjects

This study included lesions that were initially subjected to ESD as an expanded indication and were diagnosed as undifferentiated-type carcinoma (sig, por, sig-por) histologically from July 2005 to December 2016 at this hospital.

The exclusion criteria were as follows:

1. Lesions in the remnant stomach or gastric tube (due to technical difficulties and the influence on curative results) [21–23]
2. Piecemeal resection and additional resection after ESD (due to the difficulty in pathological diagnosis)
3. Unclear pretreatment biopsy results in medical records
4. Pathological diagnosis not performed at our hospital (because of integration of the pathological criterion)
5. Multiple biopsies (to avoid pathological diagnosis bias, which is dependent on the number of biopsies performed)
6. Absence of high magnification in ME-NBI and poor image quality due to the presence of mucus, clots, halation, etc. (because of the difficulty in image analysis)

Methods

Lesions were selected from the database and classified into 2 groups, MIXED-POR and PURE-SIG, according to their final histological diagnosis. Both groups were compared using pretreatment biopsy and ME-NBI findings. ME-NBI findings were classified into 2 categories, the "Presence of irregular vessels" and "Absence of irregular vessels." The presence of irregular vessels included a corkscrew pattern (defined by isolated disordered quality) [16, 19] and wavy microvessels (vessels that formed curves or spirals without being connected) [16, 18]. The absence of irregular vessels included lesions containing only the extended intervening part, defined by wider spaces between crypts in the cancerous mucosa than in the surrounding noncancerous mucosa without irregular vessels (Fig. 1). Two specialists of the Japanese Gastrointestinal Endoscopy Society retrospectively analyzed ME-NBI findings from electronic records. In case of discrepancy of opinion, mutually consensual findings were adopted.

For the biopsy, we defined lesions that were detected as poorly differentiated adenocarcinoma as pretreatment MIXED-POR. We compared posttreatment MIXED-POR and posttreatment PURE-SIG and defined the dominant finding (regular vessels or irregular vessels) in MIXED-POR as pretreatment MIXED-POR for ME-NBI.

The diagnostic accuracy of biopsy and ME-NBI was compared using ME-NBI findings that were significantly dominant in MIXED-POR or PURE-SIG. After analyzing the breakdown of biopsy and ME-NBI in each final histological diagnosis group, we compared the sensitivity, specificity, and accuracy of biopsy alone to those of the combination method of biopsy and ME-NBI.

The rate of pretreatment MIXED-POR diagnosed as posttreatment histological MIXED-POR was defined as sensitivity, while the rate of pretreatment PURE-SIG diagnosed as posttreatment histological PURE-SIG was defined as specificity. The total rate of pretreatment MIXED-POR diagnosed as posttreatment histological MIXED-POR and pretreatment PURE-SIG diagnosed as posttreatment histological PURE-SIG was defined as accuracy.

Procedures of Endoscopic Diagnosis for Gastric Cancer in Routine Medical Care

At our institute, all gastric cancers are diagnosed by endoscopy specialists in gastric cancer. The endoscopists detect and diagnose gastric cancer using white light images and chromoendoscopy us-

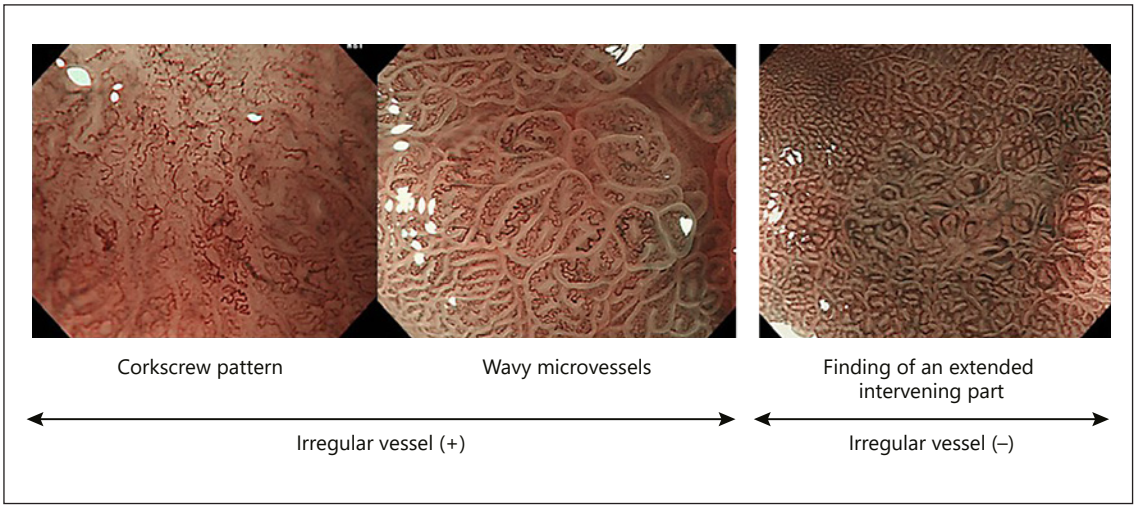

Fig. 1. ME-NBI findings of undifferentiated-type early gastric cancer. This figure was used with permission from the publisher [16, 19]. Corkscrew pattern and wavy microvessels, defined as ME-NBI findings of undifferentiated-type carcinomas. ME-NBI, magnifying endoscopy with narrow-band imaging.

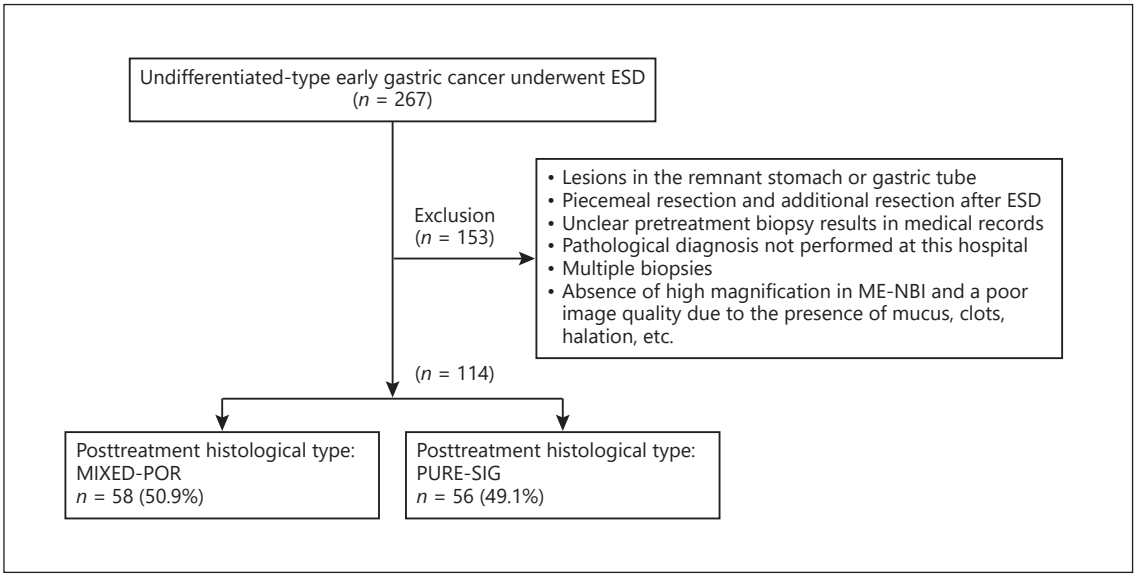

Fig. 2. Patient flowchart. ESD, endoscopic submucosal resection; ME-NBI, magnifying endoscopy with narrow-band imaging; MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma.

ing indigo carmine. Following this, the demarcation is checked under low magnification with NBI. Finally, the histological type is diagnosed using high magnification with NBI.

Endoscopic Devices

A magnifying endoscope (GIF-Q240Z, GIF260Z, and GIF290Z; Olympus Medical Systems, Tokyo, Japan) was used. In magnification examination, a soft hood (12602 and 11302; Olympus Medical Systems, Tokyo, Japan) was set up at the tip of the endoscope to enable mucosal fixation at a distance of approximately 2 mm.

Pathological Diagnosis

All lesions were diagnosed by specialists in gastrointestinal tract pathology at our institution and evaluated pathologically to integrate the pathological criterion. Pathologists re-evaluated the biopsy specimens that were collected in other institutions. Endoscopists biopsied the specimens in cases where obtaining a previous biopsy specimen was difficult or when initial biopsy had not been performed. All resected specimens after ESD were diagnosed by pathologists according to the Japanese Classification of Gastric Carcinoma, 14th edition [24]. Specimens of ESD were separated at

2.0-mm intervals, and the maximum tumor diameter, histological type, maximum invasion depth, ulceration, horizontal vertical margin, and lymphovascular invasion were evaluated. Curability was evaluated according to the Japanese Gastric Cancer Treatment Guidelines 2018 (ver. 5) [3]. Lesions were regarded as eCura B when all of the following conditions were fulfilled: pT1a, tumor size ≤2 mm, absence of ulceration (UL0), no lymphovascular invasion, and negative margin. Lesions that did not fulfill these conditions were classified as endoscopic curability C (eCura C-2).

Statistical Analysis

Comparison between the 2 groups was performed using a χ^2 test. Comparison of the examination methods was performed using McNemar's test. Statistical significance was set at $p < 0.05$. JMP Pro program (version 13; SAS Institute, Cary, NC, USA) was used for all statistical processing.

Results

We extracted 267 lesions that were initially subjected to ESD as an expanded indication and were diagnosed histologically as undifferentiated-type carcinoma (sig, por, sig-por) after ESD from July 2005 to December 2016. After excluding 153 lesions according to the exclusion criteria, 114 lesions were finally analyzed. In posttreatment histological diagnosis, 58 lesions (50.9%) were diagnosed as MIXED-POR and 56 (49.1%) as PURE-SIG (Fig. 2).

Table 1 shows the background of patients, endoscopic findings, pretreatment biopsy, and posttreatment histological diagnosis. Overall, 21.9% of the lesions were diagnosed as MIXED-POR using pretreatment biopsy. Using ME-NBI, irregular vessels with a corkscrew pattern were seen in 33.3% of lesions, and wavy microvessels were seen in 20.2% of lesions.

Table 2 shows a comparison of pretreatment biopsy and ME-NBI findings for the posttreatment histological MIXED-POR and PURE-SIG groups. Using biopsy, MIXED-POR was detected in 41.4% of the posttreatment histological MIXED-POR group lesions, and PURE-SIG was detected in 1.8% of the posttreatment histological MIXED-POR group lesions. Lesions detected at pretreatment as MIXED-POR were more likely to be confirmed as posttreatment histological MIXED-POR group lesions than as posttreatment histological PURE-SIG group lesions, and the difference was statistically significant ($p < 0.0001$). Irregular vessels were seen in 82.8% of the posttreatment histological MIXED-POR group. Irregular vessels were more likely to be seen in the posttreatment histological MIXED-POR group than in the posttreatment histological PURE-SIG group, and this result was also statistically significant ($p < 0.0001$).

Table 1. Patient characteristics and results of endoscopic submucosal resection

	Posttreatment histological type (n = 114)	
	MIXED-POR	PURE-SIG
n (%)	58 (50.9)	56 (49.1)
Age (average ± SD), years	62.5±11.9	56.5±11.7
Sex, *n* (%)		
Male	35 (60.3)	35 (62.5)
Macroscopic type, *n* (%)		
Elevated type	0 (0)	1 (1.8)
Flat type	3 (5.2)	15 (26.8)
Superficial depressed type	55 (94.8)	40 (71.4)
Location, *n* (%)		
Upper region	7 (12.1)	8 (14.3)
Middle region	38 (65.5)	28 (50.0)
Lower region	13 (22.4)	20 (35.7)
Biopsy, *n* (%)		
MIXED-POR	24 (41.4)	1 (1.8)
PURE-SIG	34 (58.6)	55 (98.2)
ME-NBI		
Irregular vessel (+), *n* (%)	48 (82.8)	13 (23.2)
Corkscrew pattern	30	8
Wavy microvessels	18	5
Irregular vessel (−), *n* (%)	10 (17.2)	43 (76.8)
Finding of an extended intervening part	10	43
Tumor size (average ± SD), mm	12.2±6.0	6.9±4.6
Depth, *n* (%)		
Intramucosal	53 (91.4)	55 (98.2)
Submucosal	5 (8.6)	1 (1.8)

MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma; SD, standard deviation; ME-NBI, magnifying endoscopy with narrow-band imaging.

Figure 3 shows a breakdown of the results of the biopsy and ME-NBI in each posttreatment histological group. Of the 58 lesions confirmed histologically to be MIXED-POR, 34 were diagnosed as PURE-SIG using biopsy. However, of these 34 lesions, irregular vessels were detected in 26 lesions using ME-NBI, suggesting that ME-NBI may lead to a MIXED-POR diagnosis when biopsy alone fails to detect it.

Figure 3 suggests that diagnosis of irregular vessels using ME-NBI contributed to the pretreatment diagnosis of MIXED-POR. Figure 4 shows the algorithm of pretreatment diagnosis using biopsy and ME-NBI. In this method, any case diagnosed as MIXED-POR by biopsy and/or irregular vessels by ME-NBI is defined as pretreatment MIXED-POR, whereas that diagnosed as PURE-SIG by biopsy and without irregular vessels by ME-NBI is de-

Table 2. Comparison of biopsy and ME-NBI findings in each posttreatment histological type group (χ^2 test)

	Posttreatment histological type		*p* value
	MIXED-POR (*n* = 58)	PURE-SIG (*n* = 56)	
Biopsy, *n* (%)			
MIXED-POR	24 (41.4)	1 (1.8)	<0.0001
PURE-SIG	34 (58.6)	55 (98.2)	
ME-NBI, *n* (%)			
Irregular vessel (+)	48 (82.8)	13 (23.2)	<0.0001
Irregular vessel (–)	10 (17.2)	43 (76.8)	

MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma; ME-NBI, magnifying endoscopy with narrow-band imaging.

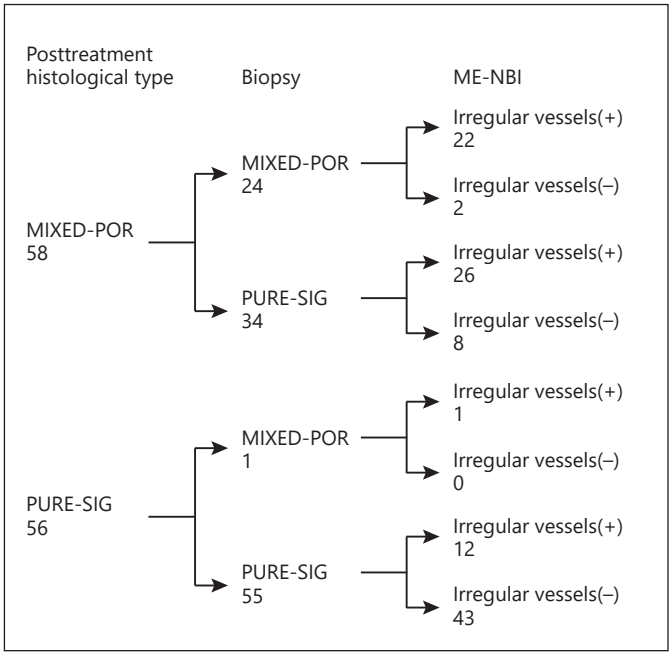

Fig. 3. Results of biopsy and ME-NBI in each posttreatment histological type group. ME-NBI, magnifying endoscopy with narrow-band imaging; MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma.

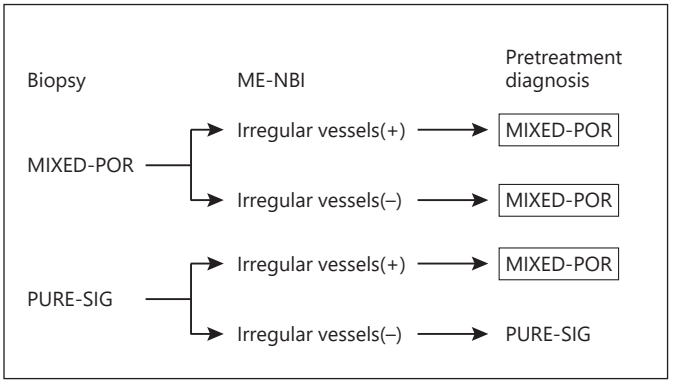

Fig. 4. Algorithm of pretreatment diagnosis with biopsy and ME-NBI. ME-NBI, magnifying endoscopy with narrow-band imaging; MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma.

fined as pretreatment PURE-SIG. Table 3 shows the comparison of diagnoses by the combination method of biopsy and ME-NBI according to our algorithm in each posttreatment histological group. Using this algorithm, we found that the cases diagnosed as pretreatment MIXED-POR were significantly common in posttreatment MIXED-POR.

Next, we compared the sensitivity, specificity, and accuracy of biopsy alone to those of the combination method to verify the additional advantages of the combination method against biopsy alone (Table 4). The sensitivity and accuracy of the combination method were significantly higher ($p < 0.05$), whereas the specificity of biopsy alone was significantly higher ($p < 0.05$).

Discussion/Conclusion

In this study, we independently used biopsy and ME-NBI to detect the MIXED-POR lesions before ESD in order to assess each method's rate of detection of these lesions, and we analyzed any additional advantages of the combination method of biopsy and ME-NBI against biopsy alone. To the best of our knowledge, no study has yet reported the efficacy of biopsy and ME-NBI as a combination method for diagnosis in undifferentiated EGCs.

Table 3. Detection rates of MIXED-POR lesions by biopsy and the combination method of biopsy and ME-NBI (χ^2 test)

	Posttreatment histological type		*p* value
	MIXED-POR (*n* = 58)	PURE-SIG (*n* = 56)	
Pretreatment diagnosis by biopsy and ME-NBI, *n* (%)			
MIXED-POR	50 (86.2)	13 (23.2)	<0.0001
PURE-SIG	8 (13.8)	43 (76.8)	

Pretreatment diagnosis "MIXED-POR," biopsy "MIXED-POR," and/or ME-NBI "irregular vessels." Pretreatment diagnosis "PURE-SIG," biopsy "MIXED-POR," and ME-NBI "irregular vessels." MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); PURE-SIG, pure signet ring cell carcinoma; ME-NBI, magnifying endoscopy with narrow-band imaging.

Table 4. Comparison of the accuracy, sensitivity, and specificity between biopsy and combination method in the MIXED-POR group (McNemar's test)

	Biopsy (95% CI)	Biopsy + ME-NBI (95% CI)	*p* value
Sensitivity	41.4% (29.6–54.2)	86.2% (75.1–92.8)	<0.0001
Specificity	98.2% (90.6–99.7)	76.8% (64.2–85.9)	0.0005
Accuracy	69.3% (60.3–77.0)	81.6% (73.5–87.6)	<0.0001

Each number represents sensitivity, specificity, or accuracy. Parentheses indicate the number of lesions. MIXED-POR, mixed poorly differentiated adenocarcinoma (por > sig, sig > por, por); ME-NBI, magnifying endoscopy with narrow-band imaging; 95% CI, 95% confidence interval.

Although 41.4% of posttreatment histological MIXED-POR lesions were diagnosed correctly by biopsy, 82.8% were diagnosed accurately by ME-NBI before ESD. ME-NBI was superior to biopsy in its detection capability. The breakdown results of biopsy and ME-NBI (Fig. 3) revealed that slightly fewer than 80% of the lesions diagnosed as PURE-SIG by biopsy despite posttreatment histological MIXED-POR were diagnosed as irregular vessels by ME-NBI. This is because only a small area can be evaluated by biopsy, thereby making the accurate detection of MIXED-POR lesions often impossible, depending on the area. Thus, the detection capability of biopsy alone is not satisfactory. In contrast, the whole surface of a lesion can be evaluated by ME-NBI, thereby making its detection capability superior. Therefore, combining ME-NBI to help detect irregular vessels improves the chances of detecting MIXED-POR lesions when biopsy fails to detect them. Based on this logic, we devised the algorithm shown in Figure 4.

Furthermore, we compared the sensitivity, specificity, and accuracy to verify the additional advantages of the combination method over those of biopsy alone. Both the sensitivity and accuracy of the combination method were significantly higher ($p < 0.0001$), whereas the specificity of biopsy alone was significantly high ($p = 0.0005$). When comparing biopsy alone and the combination method based on the algorithm, the combination method was found to be significantly superior in detecting MIXED-POR lesions. We reported that the combination method of biopsy and ME-NBI was useful to distinguish between differentiated-type-predominant mixed-type EGCs and undifferentiated-type-predominant mixed-type EGCs [20]. Thus, our study also suggested the efficacy of the combination method for detecting MIXED-POR lesions in undifferentiated-type EGCs.

We reported that the treatment results of MIXED-POR were poorer than those of PURE-SIG. We also reported a difficulty in the adaptive measurement of the tumor size, invasion depth, and ulceration [12]. If MIXED-POR can be diagnosed before ESD, we can consider adding an appropriate modality that would help in the adaptive diagnosis, such as ME-NBI and endoscopic ultrasound (EUS). ME-NBI has been reported to be effective at demonstrating the tumor size [16, 25], whereas EUS is effective at demonstrating invasion depth and ulceration [26]. In this way, the accuracy of adaptive diagnosis for ESD can be improved, making it possible to select the appropriate treatment method. The combination method suggested in this study showed higher sensitivity and accuracy than biopsy alone. Furthermore, pretreatment diagnosis of MIXED-POR is useful in daily practice as it may result in improved rates of eCura B. However, some limitations of the currently available modalities have been reported. For instance, the accuracy of demarcation diagnosis by ME-NBI has been reported to be about 80% [16, 25], and the diagnosis of ulceration and invasion depth is difficult by EUS in undifferentiated-type cancers [27–29]. Therefore, new diagnostic modalities are desired in the future.

This study has some limitations. It was a retrospective study conducted in a single institution, which could introduce bias. Furthermore, there is a possibility of a varied final diagnosis by endoscopists and pathologists. Some cases were examined by ME-NBI without maximum magnification. Surgical cases were not analyzed. To eliminate these limitations, a future prospective study including more cases and using maximum magnification in multiple facilities is desired. However, our results can

serve as basic data for comparison with future studies when a new modality is developed because these cases were accumulated in a cancer specialty institution over 10 years. Therefore, the findings of this study would be beneficial in clinical practice.

In conclusion, irregular vessels were diagnosed by ME-NBI in undifferentiated-type EGCs. When using a combination method of biopsy and ME-NBI, the rate of correct diagnosis of MIXED-POR lesions increased compared to that with biopsy alone. Thus, combining biopsy and ME-NBI may contribute to improved accuracy of pretreatment diagnosis before ESD in undifferentiated-type cancer.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) of Cancer Institute Hospital (IRB No. 2017-1033) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants involved in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.H. contributed to conception and design; M.I. and Y.H. analyzed and interpreted the data; M.I. and Y.H. drafted the article; Y.H., N.Y., S.Y., A.I., T.Y., T.H., T.T., Y.I., and J.F. critically revised the article for important intellectual content; and Y.H., N.Y., S.Y., A.I., T.Y., T.H., T.T., Y.I., and J.F. gave final approval of the article. All authors read and approved the final manuscript.

Data Availability Statement

The data are not available for public access because of patient privacy concerns but are available from the corresponding author on reasonable request.

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