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Low Discrepancy Between Tissue Biopsy Plus Magnifying Endoscopy With Narrow-Band Imaging and Endoscopic Resection in the Diagnosis of Gastric Epithelial Neoplasia (STROBE)

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Abstract: Tissue biopsy is often not very accurate for the diagnosis of gastric epithelial neoplasia (GEN), and the results differ notably from endoscopic resection (ER) in terms of the pathological diagnosis. The aims of this study were to evaluate the diagnostic performances of biopsy, magnifying endoscopy with narrow-band imaging (ME-NBI), and biopsy plus ME-NBI for GEN.

This study retrospectively analyzed 101 cases diagnosed as GEN using ER samples. The discrepancies between biopsy and ER, as well as between biopsy plus ME-NBI and ER in the diagnosis of GEN were evaluated. Factors that contributed to such discrepancies were analyzed. The sensitivity and specificity of biopsy and ME-NBI for the diagnosis of high-grade neoplasia (HGN) were determined.

The discrepancy in the pathological diagnosis between biopsy and ER was 39.6% for GEN and 54.2% for HGN. The discrepancy between biopsy combined with ME-NBI and ER was 15.9% for GEN and 10.2% for HGN. Factors that undermined the diagnostic accuracy of biopsy included the lesion size (≤10 mm, odds ratio [OR] 1; 10–20 mm, OR 0.2, 95% confidence interval [CI] 0.1–0.7; >20 mm, OR 0.5, 95% CI 0.1–2.1, $P = 0.03$) and the number of biopsy fragments (OR 0.6, 95% CI 0.5–0.8, $P = 0.001$). The sensitivity and specificity for HGN were 45.8% (33.7%–58.3%) and 100% (87.5%–100%) for biopsy, and 88.1% (77.5%–94.1%) and 92.9% (81.0%–97.5%) for ME-NBI, respectively.

In conclusion, biopsy-based diagnoses for GEN should be interpreted with caution. Biopsy combined with ME-NBI can contribute to the diagnosis of GEN, which improves diagnostic consistency with pathological result of ER specimens.

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Abbreviations: CI = confidence interval, ER = endoscopic resection, ESD = endoscopic submucosal dissection, GEN = gastric epithelial neoplasia, HGN = high-grade neoplasia, LGN = low-grade neoplasia, ME-NBI = magnifying endoscopy with narrow-band imaging, OR = odds ratio.

INTRODUCTION

Gastric cancer is a malignancy that starts in the gastric mucosa and represents a major health hazard. Gastric cancer is the fourth most commonly diagnosed cancer worldwide and the second leading cause of cancer deaths.[1] Japanese and European statistics show that the 5-year survival rate after tumor resection in patients with early gastric cancer is >90%.[2,3] Timely discovery, accurate diagnosis, and proper management of gastric epithelial neoplasia (GEN), including low-grade neoplasia (LGN) and high-grade neoplasia (HGN), are therefore important for the early diagnosis and treatment of gastric cancer. Currently, the clinical management of GEN is chiefly based on the Vienna classification of gastrointestinal epithelial neoplasia. Different clinical interventions are recommended, depending on various tissue biopsy results according to the Vienna classification.[4,5] Therefore, biopsy is particularly important as it determines the subsequent treatment plan. However, studies have reported that the discrepancy between biopsy and endoscopic resection (ER) for the diagnosis of GEN and early gastric cancer was 27.1% to 44.5%.[6–9] A considerable portion of lesions cannot be correctly diagnosed with tissue biopsy, which makes the choice of the right treatment difficult. Therefore, it is necessary to improve the accuracy of biopsy. With the development of endoscopic techniques, magnifying endoscopy with narrow-band imaging (ME-NBI) has been widely used for the diagnosis of stomach diseases, especially in the early diagnosis of gastric cancer. ME-NBI has been proven to be highly efficient in the early diagnosis of gastric cancer and has been referred to as an ''optical biopsy.''[10] This study was designed to respectively evaluate the diagnostic performances of biopsy, ME-NBI, and biopsy plus ME-NBI for GEN and to analyze the factors that affect the accuracy of biopsy.

PATIENTS AND METHODS

Subjects and Basic Information of the Study

This study was performed at the Digestive Endoscopy Center, Nanfang Hospital, Guangzhou, China. We performed a retrospective review of the cases of GEN, including LGN and HGN, as confirmed by samples from ER, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), at this center between 2008 and 2014. This study

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focused research subjects on gastric neoplasia cases diagnosed by ER within this period. Pathological diagnosis of GEN was based on the revised Vienna classification,[4,5] including mucosal LGN and HGN. Biopsy and ME-NBI were conducted prior to ER. Time interval among tissue biopsy, ME-NBI, and ER was within a week. A GIF-H260Z or GIF-Q240Z endoscope (Olympus, Tokyo, Japan) was used. This study was approved by the ethics committee of Nanfang Hospital, Guangzhou. All of the patients signed informed consent forms prior to any endoscopic procedure.

ME-NBI, Tissue Biopsy, and ER

The endoscopists at our endoscopic center have built extensive experience from gastroscopic diagnosis and treatment of >5000 cases. Endoscopists assessed the morphological features of the suspected lesions, including lesion size, and conducted ME-NBI and biopsy on suspected early gastric lesions. For suspected early gastric cancer, including protruded type (0–I type), flat type (0–IIb type), superficial elevated type (0–IIa type), superficial depressed type (0–IIc type), and depression type (0–III type), ME-NBI was performed first to evaluate the nature of the lesion. If the lesion was well-defined and associated with an abnormal vascular network or abnormal mucosal surface structure, it was diagnosed endoscopically as gastric cancer.[11,12] Biopsies were performed for all suspected lesions. A biopsy fragment was usually collected for lesions <1 cm. For lesions >1 cm, 2 to 5 biopsy fragments were harvested, depending on the lesion size. Subsequent treatment protocols were determined according to the biopsy results and endoscopic features on the ME-NBI. The treatment plans were determined by the Vienna classification of gastrointestinal epithelial neoplasia.[4,5] Biopsy results of some lesions suggested inflammation or atrophy and LGN; however, if early gastric cancer was highly suspected based on the ME-NBI results, ER was performed after full communication with the patients to establish a definite diagnosis, otherwise such patients were closely followed-up. Pathological assessment of biopsy samples and ER specimens was performed by a professional pathologist by following the Vienna classification of gastrointestinal epithelial neoplasia.

Clinical Data Collection

We retrospectively collected the following data on patients: age, sex, morphology of lesion on white light endoscopy, features on ME-NBI, lesion size, number of biopsy fragments, and pathological diagnoses of biopsy samples and ER (EMR/ESD) specimens.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 for Windows software (SPSS Inc, Chicago, IL). Quantitative variables distributed normally were compared using the Student t test, whereas categorical variables were compared using the χ^2 test. Data that were not distributed normally were analyzed using the Mann-Whitney U test. Univariate and multivariate analyses were performed to determine factors that may lead to a discrepancy in the pathological diagnosis between biopsy and ER, and the odds ratios (ORs) and 95% confidence intervals (CIs) of statistically significant factors were calculated. The sensitivity and specificity of tissue biopsy and ME-NBI for the diagnosis of HGN were determined. Pathological assessment of ER samples was used as the gold standard for diagnosis. Two-sided $P < 0.05$ were considered statistically significant.

RESULTS

Discrepancy in Pathological Diagnosis Between Biopsy Samples and ER Specimens

As shown in Table 1, this study included a total of 101 cases of GEN, including 59 cases of HGN. The discrepancy between biopsy samples and ER specimens was 39.6% for the diagnosis of GEN and 54.2% for the diagnosis of HGN. The biopsy results showed that there were 12 cases of inflammation or atrophic gastritis, whereas pathological analysis of the ER samples suggested that there were 8 cases of LGN and 4 cases of HGN. The biopsy results showed that there were 62 cases of LGN, whereas pathological analysis of the ER samples suggested that there were 28 cases of HGN. The biopsy results revealed that there were 27 cases of HGN, which were pathologically proven as HGN after ER.

Discrepancy in Pathological Diagnosis Between Biopsy Combined With ME-NBI and ER

In this study, ME-NBI was considered as an optical biopsy. If a lesion showed typical features of gastric cancer on ME-NBI, the lesion was diagnosed as early gastric cancer (also HGN). As shown in Table 2, of the 55 cases of HGN diagnosed with ME-NBI, pathological analysis after ER suggested that there were 3 cases of LGN and 52 cases of HGN. Of the 46 cases that did not present with typical ME-NBI features, pathological examination of the biopsy samples showed that there were 7 cases that were negative for dysplasia, 38 cases of LGN, and 1 case of HGN. Moreover, for these lesions, further pathological analysis of the ER samples suggested that there were 32 cases of LGN and 7 cases of HGN. Therefore, the discrepancy in the

TABLE 1. Cases Diagnosed With Biopsy or ER and Concordance in the Pathological Diagnosis Between Biopsy and ER Specimens

Pathology of Biopsy Tissue	No. of Lesions	Pathology of ER Specimen	No. of Lesions	Coincident Rate, %	Coincident Rate of HGN	Total Coincident Rate
No neoplasia (inflammation/atrophic gastritis)		LGN	8	0		
	12	HGN	4			
LGN	62	LGN	34	54.8	45.8% (27/59)	60.4% (61/101)
		HGN	28			
HGN	27	LGN	0	100		
		HGN	27			

ER = endoscopic resection, HGN = high-grade neoplasia, LGN = low-grade neoplasia, No.= number.

TABLE 2. Cases Diagnosed With Biopsy Plus ME-NBI and Concordance in the Pathological Diagnosis Between the Biopsy Plus ME-NBI and ER Procedures

ME-NBI and Pathology of Biopsy Tissue	Numbers of Lesions	Pathology of ER Specimen	Numbers	Coincident Rate of HGN	Total Coincident Rate
ME-NBI (+)+ forceps biopsy (−/+)*	55	LGN	3		
		HGN	52		
ME-NBI (−)+ forceps biopsy†					
No neoplasia	7	LGN	7	89.8% (53/59)	84.1% (85/101)
LGN	38	LGN	32		
		HGN	6		
HGN	1	HGN	1		

ER = endoscopic resection, HGN = high-grade neoplasia, LGN = low-grade neoplasia, ME-NBI = magnifying endoscopy with narrow-band imaging.
* The ME-NBI results are positive for HGN, and biopsy results are negative or positive.
† The ME-NBI results are negative for HGN, and further diagnosis of lesion does depend on the pathology of tissue biopsy samples.

pathological diagnosis between biopsy combined with ME-NBI and ER was 15.9% for gastric neoplasia and 10.2% for HGN.

Factors Influencing the Discrepancy in the Pathological Diagnosis Between Biopsy and ER

Four factors, including lesion size, number of biopsy fragments, lesion morphology, and lesion site, were examined in this study for their influence on the diagnostic discrepancy between biopsy and ER using univariate and multivariate analyses. The results showed that lesion size was an influencing factor, with the OR value for a lesion size $\leq$1 cm, between 1 and 2 cm, and >2 cm being 1, 0.2 (95% CI 0.1–0.7), and 0.5 (95% CI 0.1–2.1), respectively ($P = 0.03$). In addition, the number of biopsy fragments was also an influencing factor (OR 0.6, 95% CI 0.5–0.8, $P = 0.001$). The morphology and site of the lesions had no significant effects on the discrepancy in pathological diagnosis (Table 3). Figure 1 shows 2 cases of HGN, which were downgraded by biopsy. One of the 2 cases had a lesion >2 cm and was diagnosed as LGN by tissue biopsy. It presented with typical characteristics of gastric cancer on ME-NBI and was diagnosed as HGN after ER. The other case had a lesion <1 cm and was suggested as LGN by tissue biopsy. It presented with the typical characteristics of gastric cancer on ME-NBI and was diagnosed as HGN after pathological analysis of the ER samples.

Diagnostic Performance of Biopsy and ME-NBI for High-Grade Gastric Neoplasia

Tables 4 and 5 show high-grade gastric neoplasia diagnosed with ME-NBI and biopsy, respectively. Table 6 shows the sensitivity and specificity of ME-NBI and biopsy for the diagnosis of high-grade gastric neoplasia. The sensitivity and specificity were 88.1% and 92.9% for ME-NBI, and 45.8% and 100% for biopsy, respectively.

TABLE 3. Factors that Contribute to the Discrepancy in the Pathological Diagnosis Between Biopsy and ER

	Univariate Analysis			Multivariate Analysis		
	Coincident Cases	Noncoincident Cases	*P*	OR	95% CI	*P*
Size in diameter†			0.001			0.03
≤10 mm	7/25 (28%)	18/25 (72%)		1 (reference)		
10–20 mm	42/58 (72.4%)	16/58 (27.6%)		0.2	0.1–0.7	0.01
>20 mm	12/18 (66.7%)	6/18 (33.3%)		0.5	0.1–2.1	0.34
No. of biopsy fragments*	3 (3)	2 (1)	0.001	0.6	0.5–0.8	0.001
Location of lesion‡			0.57			
Gastric fundus/lesser curvature of stomach/greater curvature/ gastric angle/gastric antrum	3/7 (43%)/ 8/13 (62%)/ 3/4 (75%) /6/7 (86%)/ 41/70 (59%)	4/7 (57%)/ 5/13 (39%)/ 1/4 (25%)/ 1/7 (14%)/ 29/70 (41%)				
Macroscopic type of lesion‡			0.43			
0-I/IIa/IIb/IIc/IIa+IIc	1/2 (50%)/ 20/28 (71%)/ 9/16 (56%)/ 8/18 (44%)/ 23/37 (62%)	1/2 (50%)/ 8/28 (29%)/ 7/16 (44%)/ 10/18 (56%)/ 14/37 (38%)				

CI = confidence interval, ER = endoscopic resection, OR = odds ratio.
* Median (interquartile range).
† Pearson χ^2 test.
‡ Fisher exact test.

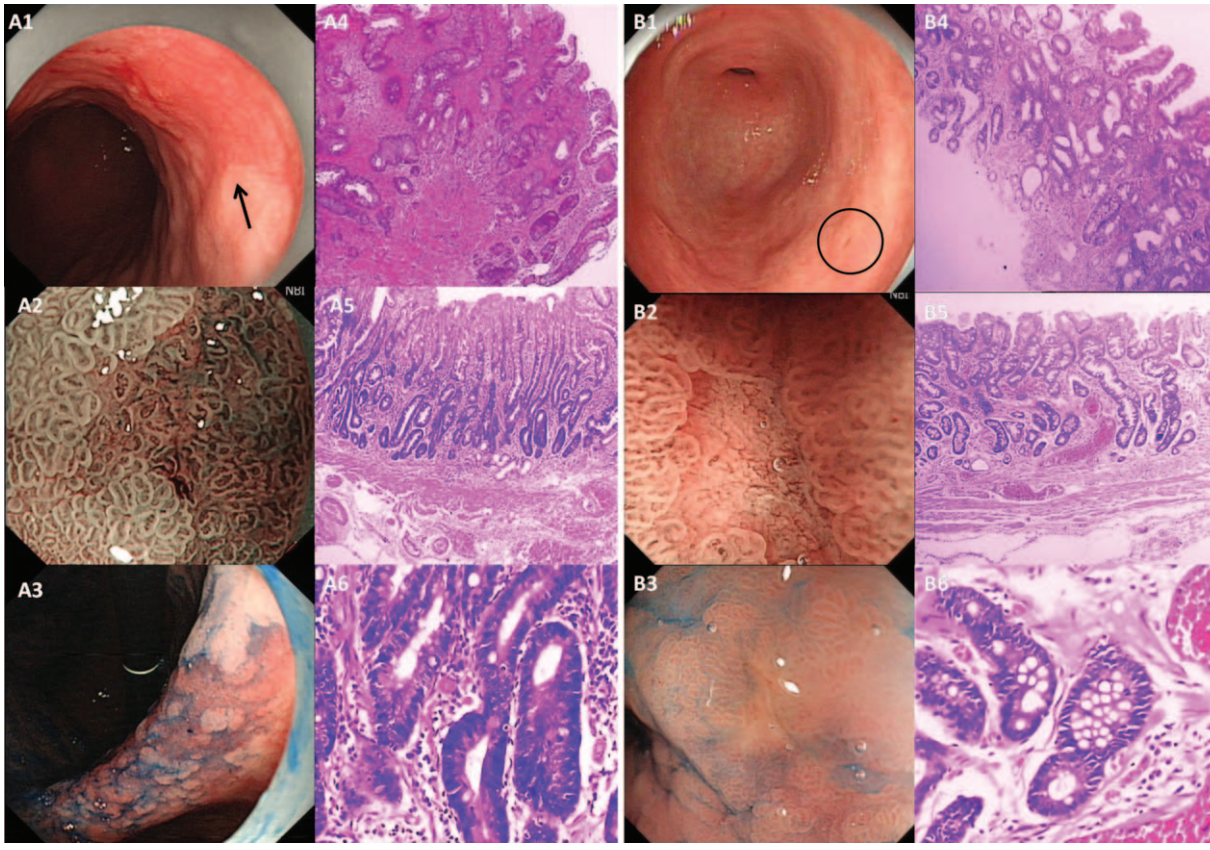

FIGURE 1. Two cases of high-grade gastric neoplastic lesions >2 cm (case A) and <1 cm (case B). Biopsy and ESD yield different pathological diagnoses in these 2 cases. (A1 and B1) morphological characteristics of cases A and B on white light endoscope; (A2 and B2) typical features of gastric cancer on ME-NBI; (A3 and B3) Indigo carmine staining; (A4 and B4) pathology of tissue biopsy samples, which show LGNs; (A5, A6, B5, and B6) pathology of ESD specimens, which show HGNs. ESD = endoscopic submucosal dissection, HGN = high-grade neoplasia, LGN = low-grade neoplasia, ME-NBI = magnifying endoscopy with narrow-band imaging.

Recommended Diagnosis and Treatment Process

This study compared the sensitivity and specificity of ME-NBI and biopsy for the diagnosis of high-grade gastric neoplasia. ME-NBI yielded a high sensitivity and a relatively low specificity, whereas biopsy had a low sensitivity and a high specificity. There was a large discrepancy in the pathological diagnosis between biopsy and ER. With this in mind, we recommend that the combination of biopsy and ME-NBI is considered for the diagnosis of suspected lesions in order to reduce missed diagnoses and misdiagnoses of HGN. If biopsy does not suggest HGN whereas ME-NBI shows typical features of gastric cancer, ER should still be considered to establish a definite diagnosis and determine proper treatment options. In this study, 55 cases had the typical characteristics of gastric cancer on ME-NBI, of which 52 cases were confirmed as HGN by pathological analysis after ER. If the ME-NBI results are negative, treatment options may be determined based on the biopsy results by following the Vienna classification of gastrointestinal epithelial neoplasia. However, it should be noted that a certain percentage of biopsy-proven LGN may be identified as HGN after ER. In this study, 38 cases did not show the typical characteristics of gastric cancer on ME-NBI and were diagnosed as LGN by biopsy; however, pathological analysis after ER suggested that there were 6 cases of HGN. Therefore, particular attention is needed for biopsy-proven LGN, and ER or close follow-up should be performed. Figure 2 shows the recommended diagnosis and treatment process as well as the number of cases included in this study.

TABLE 4. ME-NBI Diagnosis of HGN (n = 101)

	Pathology of ESD Specimen	
	HGN	Non-HGN
ME-NBI		
ME-NBI (+)	52	3
ME-NBI (−)	7	39

ESD = endoscopic submucosal dissection, HGN = high-grade neoplasia, ME-NBI = magnifying endoscopy with narrow-band imaging.

DISCUSSION

The present study demonstrated that there was a large discrepancy between tissue biopsy and ER for the diagnosis of GEN. A lesion size that was too small (≤1 cm) or too large (>2 cm) and the number of biopsy fragments were factors that undermined the accuracy of the biopsy. ME-NBI could identify early gastric cancer effectively and help to reduce the rate of misdiagnosis by biopsy.

TABLE 5. Tissue Biopsy Diagnosis of HGN (n = 101)

	Pathology of ESD Specimen	
	HGN	**Non-HGN**
HD		
HGN	27	0
Non-HGN	32	42

ESD = endoscopic submucosal dissection, HD = histopathological diagnosis, HGN = high-grade neoplasia.

Generally, biopsy is considered the gold standard for disease diagnosis. White light endoscopy identifies suspicious lesions, and biopsy establishes a definite diagnosis. Subsequent treatment programs are determined based on the Vienna classification of gastrointestinal epithelial neoplasia:[4,5] follow-up or endoscopic therapy is recommended for LGN, whereas ER or surgical resection is recommended for HGN. This study included 101 cases of GEN, including LGN and HGN, and the discrepancy in the pathological diagnosis between biopsy and ER was 39.6%, which is consistent with the discrepancy rates reported previously.[6–9] Lee et al[6] have shown that the discrepancy between biopsy and ER was 44.5%. Their study revealed that the discrepancy rates between biopsy and ER were higher for GEN than for gastric cancer (36.6% vs 7.0%, $P < 0.001$). In addition, Lim et al[9] have shown that the discrepancy between endoscopic forceps biopsy and ER for GEN was 31.7% and that 23.9% of the lesions were downgraded by biopsy compared with ER. Of the 101 cases of GEN in this study, 40 cases were downgraded by biopsy. The discrepancy between biopsy and ER for GEN may be associated with the lesion size and the number of biopsy fragments. Our current study showed that a lesion <1 or >2 cm may affect the accuracy of the biopsy results. Various studies have reported that a large lesion size is a factor affecting the accuracy of biopsy results.[9,13] This finding may be related to the characteristics of the lesion itself, as larger gastric epithelial neoplastic lesions may contain severe portions focally, whereas the most severe areas are not necessarily included in the samples taken from the lesions, which therefore cannot offer a true picture of disease severity. Our present study showed that a lesion size <1 cm was another factor that affected the accuracy of the biopsy. The accuracy of biopsy for lesions that are too small depends largely on the carefulness and experience of the operator as well as the open width of the biopsy forceps; oftentimes, the lesions are not collected, too few amounts of the lesions are sampled, or the depth of the biopsy is inadequate. In addition, this study showed that the number of biopsy fragments was another factor that contributed to the discrepancy between the biopsy and ER results. Studies have shown that misdiagnosis can be significantly reduced if ≥4 biopsy fragments are collected.[14,15] However, it is difficult to ensure that a large number of biopsy fragments is harvested from small lesions, and diagnoses can only be improved by increasing the accuracy of the biopsy or by using other means.

TABLE 6. Sensitivity and Specificity of Biopsy and ME-NBI for the Diagnosis of High-Grade Gastric Neoplasia

	HD From Biopsy Samples, %	ME-NBI, %
Sensitivity (95% CI)	45.8 (33.7–58.3)	88.1 (77.5–94.1)
Specificity (95% CI)	100 (87.5–100)	92.9 (81.0–97.5)

CI = confidence interval, HD = histopathological diagnosis, ME-NBI = magnifying endoscopy with narrow-band imaging.

As there is a large discrepancy between biopsy and ER results for lesions identified by biopsy as low-grade gastric neoplastic lesions, endoscopic features of the lesion can be used to gain more complete insight into the nature of the lesions. Cho et al[16] have shown that a size ≥1 cm (OR 1.93, 95% CI 1.06–3.52), depressed morphology (OR 3.81, 95% CI 1.22–11.9), and mucosal surface erythema (OR 2.49, 95% CI 1.31–4.72) were risk factors that turn low-grade GEN into HGN or cancer. Therefore, ER rather than follow-up is still recommended for low-grade gastric neoplasia with any of the above risk factors. In addition, 49% of the lesions that were diagnosed as adenomas or difficult to diagnose as regenerative or neoplastic lesions were confirmed as cancer after ER. These lesions were mostly ≥2 cm in size and showed depressed areas and ulcers.[17] ER should also be considered for these lesions to establish a definitive diagnosis.

To improve the accuracy of biopsy, a previous study used pronase to wash the mucosal surface of the lesions, which increased the depth of the biopsy, facilitated accurate positioning, and helped improve the accuracy of the biopsy.[18] In addition, Jiang et al[19] have shown that a targeted biopsy with ME-NBI could achieve a high pathological positive rate with a small quantity of tissues. However, targeted biopsy with ME-NBI increases the difficulty of the biopsy procedure. In our retrospective study, it was difficult to determine which lesions underwent targeted biopsy under ME-NBI; therefore, we did not assess the impact of targeted biopsy under ME-NBI. However, ME-NBI was performed for all of these lesions before ER. We compared the diagnostic performance of biopsy and ME-NBI for HGN and found that biopsy had a high specificity but low sensitivity, whereas ME-NBI had a high sensitivity and specificity and could identify high-grade gastric neoplasia (early gastric cancer) effectively. This study showed that the accuracy of biopsy was affected by lesion size, particularly lesions <1 cm, and ME-NBI offered a high diagnostic performance for small gastric cancer lesions.[12,20] Importantly, this study showed that the combination of biopsy and ME-NBI significantly reduced the discrepancy between biopsy and ER from 39.6% to 15.9% for GEN and from 54.2% to 10.2% for HGN.

Therefore, we recommend ER for suspected early gastric cancer to establish a definite diagnosis if the ME-NBI results are consistent with typical features of gastric cancer, even if the biopsy results are negative. However, the use of ME-NBI for determining the depth of gastric cancer has certain limitations. It is necessary to determine the depth of the lesion prior to ER. If the lesion is found to be a smooth surface protrusion, or a depressed or flat lesion, it is most likely to be an intramucosal lesion (T1m). If the lesion shows such features as an irregular nodular surface protrusion, an irregular ulcer with marginal elevation at the base, or marked depression with interrupted folds or elevation, it is most likely to be a submucosal lesion (T1sm).[21] Based on the above endoscopic features, the diagnostic performance of white light endoscopy was 73.7% for lesions in the T stage, and the diagnostic performance of endoscopic ultrasonography was 67.4%. Therefore, assessment

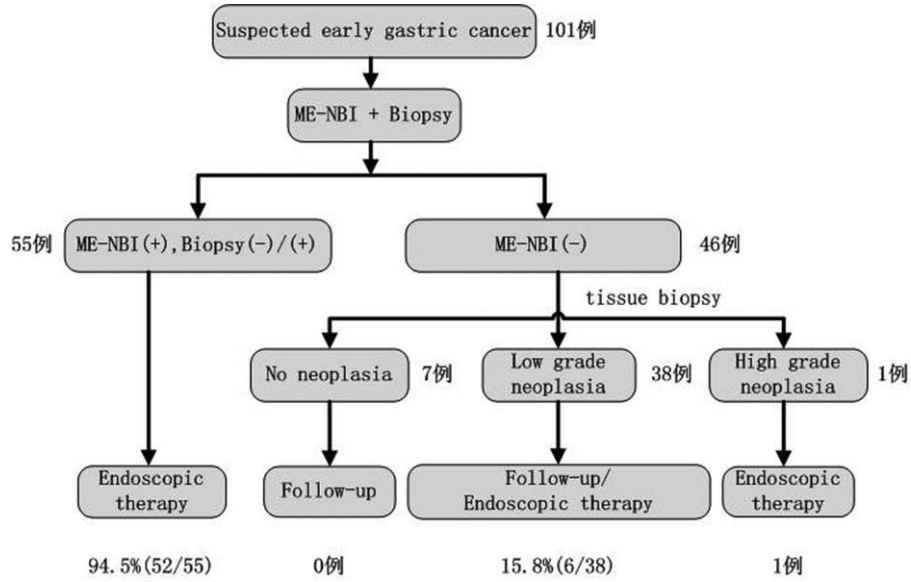

FIGURE 2. A recommended diagnosis and treatment process for suspected gastric lesions. No matter what the results of tissue biopsy (Biopsy [−]/[+]) is, while the lesion under ME-NBI shows typical features of gastric cancer, ER should still be considered to establish a definite diagnosis and determine proper treatment options. In this study, 55 cases had typical characteristics of gastric cancer on ME-NBI, of which 52 cases were confirmed as HGN by pathological analysis after ER. If the ME-NBI results are negative, treatment options may be determined based on the biopsy results by following the Vienna classification of gastrointestinal epithelial neoplasia. ER = endoscopic resection, HGN = high-grade neoplasia, ME-NBI = magnifying endoscopy with narrow-band imaging.

by endoscopic ultrasonography may have some limitations for early gastric cancer in the T stage. Previous research has reported that a lesion may be a submucosal cancer or an even deeper situated cancer if it meets the following ≥3 endoscopic features: tumor size >3 cm, marginal elevation, red color change, and irregularity on the lesion surface.[22] Endoscopic ultrasonography has been demonstrated to be highly accurate for lesions invading the submucosal layer and muscularis propria .[23] After a lesion is diagnosed by ME-NBI as early gastric cancer, it is necessary to determine the depth of the lesion using endoscopic features, and endoscopic ultrasonography can be performed if necessary.

This study suffers from some limitations. First, selection bias may exist, which is an inherent drawback of retrospective studies. Second, pathological evaluation in this study followed the Vienna classification of gastrointestinal epithelial neoplasia. This study analyzed the concordance in pathological diagnosis between biopsy and ER for HGN, but it did not examine the agreement between biopsy and ER for high-grade dysplasia, carcinoma in situ, or intramucosal carcinoma, which belong to HGN, because the information collected by this retrospective study was limited.

CONCLUSIONS

In summary, there is a large discrepancy in the pathological diagnosis of GEN between biopsy and ER, and biopsy tends to underestimate the severity of the underlying disease. Care must be exercised for suspected early gastric cancer on white light endoscopy, even if it is diagnosed by biopsy as LGN or negative for neoplasia. Tissue biopsy plus ME-NBI can provide a more comprehensive assessment of neoplastic lesions, and ER may be necessary if typical ME-NBI features are present. Due to the limitation of retrospective study, a prospective and large sample study may be necessary.

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127:2893–2917.
2. Marrero JM, Savalgi RS, McCormick C, et al. Progression of gastric mucosal dysplasia of the postgastrectomy stomach. *Surg Technol Int.* 2000;IX:333–337.
3. Ono H. Early gastric cancer: diagnosis, pathology, treatment techniques and treatment outcomes. *Eur J Gastroenterol Hepatol.* 2006;18:863–866.
4. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut.* 2000;47:251–255.
5. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut.* 2002;51:130–131.
6. Lee CK, Chung IK, Lee SH, et al. Is endoscopic forceps biopsy enough for a definitive diagnosis of gastric epithelial neoplasia? *J Gastroenterol Hepatol.* 2010;25:1507–1513.
7. Sung HY, Cheung DY, Cho SH, et al. Polyps in the gastrointestinal tract: discrepancy between endoscopic forceps biopsies and resected specimens. *Eur J Gastroenterol Hepatol.* 2009;21:190–195.
8. Jung MK, Jeon SW, Park SY, et al. Endoscopic characteristics of gastric adenomas suggesting carcinomatous transformation. *Surg Endosc.* 2008;22:2705–2711.
9. Lim H, Jung HY, Park YS, et al. Discrepancy between endoscopic forceps biopsy and endoscopic resection in gastric epithelial neoplasia. *Surg Endosc.* 2014;28:1256–1262.
10. Yao K, Doyama H, Gotoda T, et al. Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: a prospective multicenter feasibility study. *Gastric Cancer.* 2014;17:669–679.
11. Yao K, Ohishi T, Matsui T, et al. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest Endosc.* 2002;56:279–284.

12. Ezoe Y, Muto M, Horimatsu T, et al. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. *Gastrointest Endosc.* 2010;71:477–484.
13. Lee IS, Park YS, Lee JH, et al. Pathologic discordance of differentiation between endoscopic biopsy and postoperative specimen in mucosal gastric adenocarcinomas. *Ann Surg Oncol.* 2013;20:4231–4237.
14. Ren W, Yu J, Zhang ZM, et al. Missed diagnosis of early gastric cancer or high-grade intraepithelial neoplasia. *World J Gastroenterol.* 2013;19:2092–2096.
15. Tatsuta M, Iishi H, Okuda S, et al. Prospective evaluation of diagnostic accuracy of gastrofiberscopic biopsy in diagnosis of gastric cancer. *Cancer.* 1989;63:1415–1420.
16. Cho SJ, Choi IJ, Kim CG, et al. Risk of high-grade dysplasia or carcinoma in gastric biopsy-proven low-grade dysplasia: an analysis using the Vienna classification. *Endoscopy.* 2011;43:465–471.
17. Takao M, Kakushima N, Takizawa K, et al. Discrepancies in histologic diagnoses of early gastric cancer between biopsy and endoscopic mucosal resection specimens. *Gastric Cancer.* 2012;15:91–96.
18. Lee SY, Han HS, Cha JM, et al. Endoscopic flushing with pronase improves the quantity and quality of gastric biopsy: a prospective study. *Endoscopy.* 2014;46:747–753.
19. Jiang H, Tu HM, Qiao Q, et al. Effect of route of preoperative biopsy on endoscopic submucosal dissection for patients with early gastric cancer. *Asian Pac J Cancer Prev.* 2014;15:8917–8921.
20. Fujiwara S, Yao K, Nagahama T, et al. Can we accurately diagnose minute gastric cancers ($\leq$5 mm)? Chromoendoscopy (CE) vs magnifying endoscopy with narrow band imaging (M-NBI). *Gastric Cancer.* 2014[Epub ahead of print].
21. Choi J, Kim SG, Im JP, et al. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. *Endoscopy.* 2010;42:705–713.
22. Abe S1, Oda I, Shimazu T, et al. Depth-predicting score for differentiated early gastric cancer. *Gastric Cancer.* 2011;14:35–40.
23. Mouri R, Yoshida S, Tanaka S, et al. Usefulness of endoscopic ultrasonography in determining the depth of invasion and indication for endoscopic treatment of early gastric cancer. *J Clin Gastroenterol.* 2009;43:318–322.