Abstract

Background & Aims: Discrimination of gastric adenomas from adenocarcinomas by conventional endoscopy is difficult. Therefore, we evaluated the usefulness of magnifying endoscopy combined with narrow-band imaging for this differential diagnosis. Methods: Forty-nine consecutive gastric lesions were diagnosed as adenomas by conventional endoscopy with forceps biopsy and finally resected by endoscopic submucosal dissection. The findings from magnifying endoscopy with narrow-band imaging were retrospectively classified into five types according to the marginal crypt epithelium and microvascular pattern: Types I and II (clear marginal crypt epithelium combined with regular or unclear microvascular pattern) and Types III, IV, and V (unclear marginal crypt epithelium combined with regular, irregular, or unclear microvascular pattern). Results: Conventional endoscopy showed 39 flat elevated-type lesions (0–IIa) and 10 flat elevated-type lesions with depression (0–IIa+IIc). The patterns on magnifying endoscopy with narrow-band imaging were Type I (n = 8), Type II (n = 8), Type III (n = 2), Type IV (n = 30), and Type V (n = 1). The final histological diagnoses after endoscopic submucosal dissection were adenoma (n = 20), adenocarcinoma in adenoma (n = 22), and adenocarcinoma (n = 7). The cancer-bearing rates were Type I (0%), Type II (0%), Type III (100%), Type IV (89.7%), and Type V (100%). Among the expert endoscopists, intra- and interobserver κ values for each type were 0.85 each, with 92.0% and 88.0% consensus of diagnoses, respectively. Conclusions: Magnifying endoscopy with narrow-band imaging is a powerful tool for diagnosing gastric borderline lesions.

Key words

Introduction

Gastric adenomas are classified as borderline lesions because long-term follow-ups show that gastric adenomas occasionally progress to high-grade dysplasia or cancer [1, 2]; most of these are suitable for endoscopic treatment, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [1, 2]. However, it is sometimes difficult to discriminate gastric adenomas from adenocarcinomas by conventional endoscopy, and this leads to discrepancies between forceps biopsy- and resected tissue-based diagnoses.

There have been attempts to diagnose gastric lesions by observing the microstructure of a lesion with magnifying endoscopy (ME) [3]. To improve the accuracy, the combination of ME with a narrow-band imaging (NBI) system is advantageous for observing the microstructure of the gastric mucosa and microvessels [4]. However, the usefulness of ME–NBI in differentiating between cancer and adenoma in flat elevated lesions of the stomach remains unclear. This study aimed to elucidate the usefulness of ME–NBI for the differential diagnosis of gastric adenoma and carcinoma.

Methods

Patients
In our hospital, all gastric adenomas are resected endoscopically because of their malignant potential. We retrospectively examined 49 consecutive gastric lesions from 49 patients diagnosed as having adenomas by forceps...
Thus, the patterns of MCE and MVP combinations were classified into five types: Type I (clear MCE and regular MVP), Type II (clear MCE and unclear MVP), Type III (unclear MCE and regular MVP), Type IV (unclear MCE and irregular MVP), and Type V (unclear MCE and unclear MVP) (Figs. 2 and 3). The most abnormal part of each lesion was used for classification. If a lesion had multiple findings of MCE, for example clear and unclear MCE recognized in the same lesion, the finding of unclear MCE was adopted. Moreover, if a lesion had multiple findings of MVP, such as irregular MVP, regular MVP, and unclear MVP, the adopted finding was as described above in order. The endoscopic diagnoses were performed by four endoscopists (A.K, A.K, and H.B) who were experts in NBI. The recorded endoscopic findings and collected still images were reviewed retrospectively. After a tutorial on the five classified types in this study, 30 typical endoscopic images were shown twice in random order to two experienced endoscopists (A.K and H.B) who were experts in NBI and blinded to the clinical and histopathological findings. The interobserver reproducibility and level of agreement for individual images were analyzed between these two endoscopists. The same set of images was re-presented to the same endoscopist (A.K) one week later to assess intraobserver agreement. Moreover, interobserver agreement between two inexperienced endoscopists (Y.S and R.N) was reviewed twice (first, image presentation alone; second, after brief lecture) one week apart.

Assessment of endoscopic findings

Two endoscopes, GIF-Q240Z and GIF-H260Z (Olympus, Tokyo, Japan) were used in this study. The electronic endoscope system (Evis Lucera Spectrum; Olympus) used in this study incorporated both a structure enhancement function and an NBI function. The structure enhancement function of the video processor was set at a level of 4, 6, or 8 (level 4 or 6 for non-magnified observation and level 8 for magnified observation). Before treatment, conventional endoscopy was performed, and the gross morphology, histological type, and depth of the lesions were examined according to the Japanese Classification of Gastric Carcinoma [5]. If there were no findings of massive submucosal invasion, such as obvious deep depression, hardened wall, fold convergence, and non-neoplastic mucosa at the rising edge of the lesion with wall thickening or disruptions or thinning of the third layer corresponding to the submucosal layer by endoscopic ultrasound, the lesions were diagnosed as intramucosal and were eligible for endoscopic curative resection.

Next, ME–NBI was performed, and the mucosal microstructures and subepithelial microvessels were partially characterized according to the VS classification system proposed by Yao et al [6]. A black soft hood (MB-162 for GIF-Q240Z or MB-46 for GIF-H260Z, Olympus) was mounted on the tip of the endoscope to maintain a distance of 3 mm between the tip of the endoscope zoom lens and the mucosal surface. By virtue of its way, the maximum magnification endoscopic image of maximum magnification (90× on GIF-Q240Z and 85× on GIF-H260Z, on under the condition of a 19-inch monitor with full height size) could be obtained.

The mucosal microstructures were assessed based on how clearly the marginal crypt epithelium (MCE) was observed as a white marginal structure surrounding the subepithelial vessels (Fig. 1). The findings were simply classified into two categories, clear or unclear, although the VS classification defined the microsurface pattern as regular, irregular, or absent. Subepithelial capillaries (SECs) were visualized as dark brown structures by ME–NBI at intervening areas between the crypts of normal gastric mucosa. However, we defined capillaries or venules at intervening areas between the crypts of tumors as subepithelial microvessels because we could not judge a vessel precisely as a capillary in the tumor (Fig. 1). The microvascular pattern (MVP), which indicated patterns of the subepithelial microvessels, was classified into three categories: regular, irregular, and unclear. Irregular MVP was characterized by findings such as caliber change, unequal size, asymmetry, and non-uniform distribution. As above, we classified 49 lesions into six groups, but no lesions had clear MCE and irregular MVP. Thus, the patterns of MCE and MVP combinations were classified into five types: Type I (clear MCE and regular MVP), Type II (clear MCE and unclear MVP), Type III (unclear MCE and regular MVP), Type IV (unclear MCE and irregular MVP), and Type V (unclear MCE and unclear MVP) (Figs. 2 and 3). The most abnormal part of each lesion was used for classification. If a lesion had multiple findings of MCE, for example clear and unclear MCE recognized in the same lesion, the finding of unclear MCE was adopted. Moreover, if a lesion had multiple findings of MVP, such as irregular MVP, regular MVP, and unclear MVP, the adopted finding was as described above in order. The endoscopic diagnoses were performed by four endoscopists (A.K, A.K, and H.B) who were experts in NBI. The recorded endoscopic findings and collected still images were reviewed retrospectively. After a tutorial on the five classified types in this study, 30 typical endoscopic images were shown twice in random order to two experienced endoscopists (A.K and H.B) who were experts in NBI and blinded to the clinical and histopathological findings. The interobserver reproducibility and level of agreement for individual images were analyzed between these two endoscopists. The same set of images was re-presented to the same endoscopist (A.K) one week later to assess intraobserver agreement. Moreover, interobserver agreement between two inexperienced endoscopists (Y.S and R.N) was reviewed twice (first, image presentation alone; second, after brief lecture) one week apart.

Pathological examination

An expert pathologist who specialized in gastrointestinal pathology in our hospital reviewed the sections; the pathologist was blinded to the endoscopic and clinical findings. The resected specimens were evaluated according to the Vienna classification of gastrointestinal epithelial neoplasia [7], which defined gastric adenoma as category 3 (non-invasive low-grade neoplasia) and category 4.1 (non-invasive high-grade adenoma/dysplasia). Immunostaining for CD34 and Ki-67 was also performed according to standard immunohistochemical procedures.

Statistical analysis

The SAS statistical package (SAS Institute, Tokyo, Japan) was used for analysis. The Welch t-test was used to compare differences between different samples for statistical significance. The statistical significance level was set at P < 0.05. The χ2 test and pairwise κ statistic were used to analyze intra- and interobserver agreement, and κ values were interpreted according to the guidelines of Landis and Koch [8]. In brief, the greater the κ value, the stronger the agreement between the tests (variables). When the κ value ranged from 0.81 to 1.0, 0.61 to 0.8, 0.41 to 0.6, 0.21 to 0.4, or 0 to 0.2, the strength of agreement was perfect, substantial, moderate, fair, or slight, respectively.

Ethics

All endoscopic procedures were performed with the approval of our hospital ethics committee. Written informed consent was obtained from all patients for endoscopic treatment.
Results

The baseline characteristics of the 49 lesions are shown in Table I. The mean maximum diameter of the 49 lesions was 13.7 mm (range, 7–45 mm), and almost all lesions were located in the middle or lower part of the stomach (one lesion in the upper corpus, 28 lesions in the middle corpus, and 20 lesions in the lower corpus) (Table I). Thirty-nine lesions were morphologically of the flat elevated type (0–IIa) [9], and 10 lesions were of the flat elevated type with depression (0–IIa+IIc) [9]. According to our criteria for ME–NBI, the 49 lesions were classified as follows: 8 lesions as Type I, 8 lesions as Type II, 2 lesions as Type III, 30 lesions as Type IV, and 1 lesion as Type V (Fig. 2).

After resection by ESD, each sample was pathologically diagnosed. The results showed that 20 lesions were adenomas, 22 were well-differentiated adenocarcinomas in adenomas, and 7 were well-differentiated adenocarcinomas (Table I). The mean maximum diameter of the adenocarcinoma in adenomas was significantly greater than that of the adenomas (P < 0.01), and the adenocarcinomas were significantly larger than the adenomas (P < 0.01) (Table I). In all samples of adenocarcinomas, the invasion depth was within the mucosa. The cancer-bearing rates of our classification were as follows: Type I (0%), Type II (0%), Type III (100%), Type IV (89.7%), and Type V (100%) (Table II).

Among the expert endoscopists, the intraobserver κ value for each type was 0.85, with 92.0% consensus of diagnoses, which indicated perfect agreement, and the interobserver κ value was 0.85, with 88.0% consensus of diagnoses, which indicated perfect agreement. In the first examination between
the two inexperienced endoscopists, the interobserver \( \kappa \) value was 0.44, with 68.0% consensus of diagnoses, which indicated moderate agreement. In the second examination, the interobserver \( \kappa \) value was 0.79, with 84.0% consensus of diagnoses, which indicated substantial agreement (Table III). Representative images of an adenoma and an adenocarcinoma in adenoma are shown in Figs 1, 4, and 5.

As a result of the final histological examination of resected specimens by ESD, 29 of the 49 lesions that were initially suspected as adenomas by forceps biopsies were finally diagnosed as adenocarcinomas. This indicates that the accuracy of the histological diagnosis using forceps biopsy for adenomas was 40.8%. On the other hand, when ME–NBI was used combined with the diagnostic criteria that Types I and II were adenomas and Types III, IV, and V were malignant potential lesions, then the diagnostic accuracy was 87.9%.

Discussion

The treatment strategy for gastric adenoma, either a strict follow-up with forceps biopsy or endoscopic resection, remains controversial because discrimination of an adenoma from a carcinoma using conventional endoscopy with forceps

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0–IIa, flat elevated type; 0–IIa+IIc, flat elevated type with depression; tub1, well-differentiated adenocarcinoma. Comparison of tumor size between adenoma and adenocarcinoma in adenoma (*\( P < 0.01 \)) and comparison between adenoma and adenocarcinoma (†\( P < 0.01 \)). The proportion of 0–IIa+IIc was higher than that of adenoma (§\( P < 0.01 \)).
biopsy is sometimes difficult. Endoscopic findings such as a diameter greater than 1 cm, redness, and depressed morphology were previously reported as predictive factors for malignancy [2]. Histological findings are most important for the determination of malignancy, but the possibility of inappropriate selection of a biopsy site where cancer cells are not present remains. Thus, discrepancies are occasionally observed between endoscopic and histological diagnoses [1], and more advances in endoscopic technology are required. Recently, ME–NBI has improved the diagnostic accuracy for gastrointestinal neoplasms, and the number of studies reporting its usefulness for gastric epithelial lesions is increasing [3, 10-20].

Using ME–NBI, Yao et al previously reported that two factors, MCE, which is the white marginal structure surrounding the subepithelial vessels, and MVP, which is a dark brown structure derived from subepithelial microvessels, are useful for the diagnosis of early gastric cancer [6, 18]. Moreover, Maki et al stated that ME–NBI was useful in the differential diagnosis between low-grade adenoma and early gastric cancer of superficial elevated gastric lesions [21]. In this study, we simply classified the findings from ME–NBI into five types according to the combination of MCE and MVP patterns and compared them with the results of the final histological diagnosis. Types I and II, characterized by a clear MCE with regular or unclear, but not irregular, MVP, included adenoma alone. Although current guidelines recommended that all gastric adenomatous lesions should be resected [22], strict follow-up with forceps biopsy might be permissible for these lesions, which were histopathologically expected not to have a cancerous part because of its structural regularity.

Types III, IV, and V were characterized by an unclear MCE with regular, irregular, and unclear MVP, respectively. Type III lesions (n = 2) were detected by conventional endoscopy as a flat elevation with a local depression (0–IIa+IIc) [9], and the depressed area was histologically diagnosed as an adenocarcinoma. The regular MVP pattern observed in these lesions was thought to correspond to the regular ultrafine network pattern often observed in depressed adenomas described by Tamai et al [23]. Almost all Type IV lesions were diagnosed as adenocarcinomas, but four lesions were histologically diagnosed as adenomas according to immunohistochemical studies that revealed the limited distribution of Ki-67 and p53 immunoreactive cells in the upper part of the mucosa. An unclear MCE strongly suggests a diagnosis of malignant potential, but the requirement of immunohistochemical studies suggests that ME–NBI has some limitations in the diagnosis of gastric borderline lesions. Type V in our study was thought to be consistent with the image of irregular white opaque substance that Yao et al reported as commonly observed in cancer cases [19].

The malignant glands of an adenocarcinoma in adenoma are often irregular and lower in height than those of the normal mucosa, and this might be associated with unclearness of MCE. Nonaka et al suggested that not only the decrease in height of the gland but also an increased three-dimensional complexity of the structure might be related to unclearness of MCE in suspicious lesions of adenocarcinomas [24]. We agree with their opinion, but structural complexity was detected only in Type IV lesions and not in Type III lesions. MCE might be obscured by a high nucleus/cytoplasm ratio,
which could attenuate backward scattering in the cytoplasm, but that theory remains unconfirmed. Type III lesions were histologically characterized by changes in the gland density while maintaining structural regularity. Therefore, the three-dimensional complexities described by Nonaka et al may be one of the factors relevant to the magnifying endoscopic features of Type IV lesions but not of Type III lesions. We would like to consider MCE clearness as the presence of a clear white zone of regular width for a simpler indicator of microstructure. For this reason, MCE of Type III in the NBI classification of Nonaka et al was regarded as unclear and classified as Type IV according to our classification.

In our study, the diagnostic accuracy of ME–NBI (87.9%) surpassed that of conventional endoscopy with forceps biopsy (40.8%). In other words, there is a possibility that the presence or absence of cancer can be determined only by MCE, which is a very simple indicator. In addition, the good intraobserver reproducibility and interobserver reliability of MCE and MVP among the experienced endoscopists showed that our classification was simple and feasible. On the other hand, for the inexperienced endoscopists, the improved κ value after the brief lecture showed that this classification was easy to learn. This diagnostic tool may be very advantageous for elderly patients who are taking anticoagulants for ischemic heart or cerebral diseases.

The study limitations include its single-center retrospective nature and the relatively small number of cases. Variations in the endoscopes and the skill level of the operators were other limitations. Furthermore, although the most abnormal part of each lesion was used for classification in this study, there was no evidence that the most abnormal part was identical to histologically confirmed carcinoma in the final diagnosis of carcinoma in adenoma.

**Fig 4.** A case of tubular adenocarcinoma in adenoma (Type IV): (a) Conventional endoscopy shows an elevated lesion (7 × 7 mm in diameter) with a partially red colored area that was observed at the greater curvature of the antrum. (b) Magnified endoscopy with narrow-band imaging reveals an unclear marginal crypt epithelium and an irregular microvessel pattern to match the red colored area, corresponding to Type IV. (c) and (d): H&E (c, low-power field; d, high-power field). Histopathological examination showed tubular adenocarcinoma in adenoma. The adenoma components were also observed around the cancer. (e) CD34 immunostaining. Stained capillaries of the subepithelium between the crypts were irregular and had various diameters. (f) Ki-67 immunostaining. Strongly stained tumor cells were distributed from the middle layer to the surface layer of the mucosa.
Conclusion

Magnifying endoscopy-NBI was useful for the diagnosis of gastric borderline lesions. Further prospective randomized studies in which ME–NBI findings of the evaluated area are exactly compared with histopathological findings in a larger sample of patients should be conducted to confirm the usefulness of the endoscopic criteria proposed in this study.

Conflicts of interest

The authors declare that they have no conflict of interest. No benefit in any form has been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Acknowledgment

We thank our colleagues in the Shiga University of Medical Science Hospital for their assistance in writing this paper.

Fig 5. A case of adenocarcinoma in adenoma (Type IV): (a) Conventional endoscopy shows an elevated lesion (15 × 12 mm in diameter) with a depression in the center at the greater curvature of the antrum. (b) Magnified endoscopy with narrow-band imaging reveals an unclear marginal crypt epithelium and an irregular microvessel pattern in the depression, corresponding to Type IV. (c) and (d): The histological diagnosis was a well-differentiated adenocarcinoma in adenoma. (e) CD34 immunostaining. The capillaries were irregular and tortuous and had various diameters. (f) Ki-67 immunostaining. The tumor cells were distributed from the middle layer to the surface layer of the mucosa.

References