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Prospective comparison of diagnostic performance of magnifying endoscopy and biopsy for sessile serrated adenoma/polyp

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Abstract

Background Magnifying narrow-band imaging (M-NBI) has recently improved the accuracy of endoscopic diagnosis of gastrointestinal tumors, including colorectal polyps. However, it can be difficult to distinguish between sessile serrated adenoma/polyps (SSA/Ps) and other polyps, especially hyperplastic polyps (HPs), by histological biopsy, because diagnostic features of SSA/Ps can be detected around the colon crypt bases. We aimed to evaluate the accuracy of endoscopic diagnosis of SSA/Ps using M-NBI compared with histological biopsy.

Methods We prospectively enrolled patients diagnosed with SSA/Ps by preoperative endoscopy and assessed the diagnostic accuracy. The primary outcome was the diagnostic accuracy of endoscopy and biopsy.

Results Between August 2015 and October 2017, 295 lesions were resected by polypectomy or endoscopic mucosal resection, and 79 endoscopically resected specimens that were endoscopically diagnosed as SSA/P underwent biopsy for histological examination. Two lesions were excluded because the specimens were too small for histological examination. Finally, 77 endoscopically resected specimens and 77 biopsy specimens were included in the analysis. Histopathological examination showed 67 SSA/Ps, 8 HPs, and 2 adenomas. The sensitivity, specificity and accuracy of endoscopic M-NBI diagnosis for SSA/Ps were 95.7%, 95.5% and 95.6%, respectively. The sensitivity, specificity and accuracy of histological diagnosis of a single biopsy specimen were 71.6%, 90.0% and 74.0%, respectively. The McNemar test showed significant differences between biopsy and endoscopy diagnoses (P=0.001).

Conclusion This study shows that biopsy may be avoided by using M-NBI in patients with suspected SSA/Ps.

Keywords Colorectal neoplasms, colonoscopy, biopsy, diagnosis, adenomatous polyps

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Conflict of Interest: None

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Introduction

Previously, polyps presenting with serrated structures were diagnosed as hyperplastic polyps (HPs) and were not considered to be at risk for cancer. Recently, it has become clear that neoplastic lesions called sessile serrated adenoma/polyps (SSA/Ps) are present in HPs [1], and a serrated neoplastic pathway has been increasingly indicated, via which colorectal cancer can develop from serrated lesions. Hence, SSA/Ps are now considered to be lesions that require endoscopic resection [2,3]. However, SSA/Ps have much in common with HPs, morphologically and pathologically, and differentiation is often problematic in daily clinical practice.

Magnifying narrow-band imaging (M-NBI) has recently improved the performance of endoscopic diagnosis and some reports have demonstrated that it has a high potential for differentiation of SSA/Ps and other polyps [4-6]. However, because this diagnostic method is not in widespread use, biopsies are still performed for SSA.

Although some pathological diagnostic criteria for SSA/Ps have been published [1,7-11], for pathological diagnosis of a biopsy it can be difficult to distinguish between SSA/Ps and HPs, because diagnostic features of the former can be detected around the colon crypt bases. Additionally, endoscopic biopsies have been found to have several problems. For example, they are costly [12], cause fibrosis that may interfere with subsequent endoscopic treatment [13,14], and may result in delayed bleeding after biopsy [15].

However, few studies have examined the diagnostic accuracy of endoscopic diagnosis versus biopsy for SSA/Ps. Here, we prospectively compared the accuracy of M-NBI and histological biopsy of SSA/Ps.

Patients and methods

Patients

This prospective non-randomized controlled study was performed in a single municipal hospital. The study protocol was approved by the Ethics Committee of the Osaka Red Cross Hospital and complied with the Declaration of Helsinki. The study was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN-CTR) as number UMIN 000018837.

The inclusion criteria were patients aged ≥20 years with a suspected SSA/Ps of 6-20 mm in diameter on preoperative endoscopy and scheduled for endoscopic resection. Patients were excluded if they had undergone right hemicolectomy, or had symptoms suspicious of colorectal stenosis or cancer, inflammatory bowel diseases, familial polyposis, or previously biopsied lesions. Patients with suspected SSA/Ps were enrolled and assessed for diagnostic accuracy. Other polyps diagnosed as NBI International Colorectal Endoscopic Classification (NICE) types 2 and 3 were treated according to clinical practice (Fig. 1). All patients gave their written informed consent to participate.

Endoscopic procedure

All the endoscopists who participated in the study were certified by the Japan Gastroenterological Endoscopy Society and had >10 years of experience in endoscopic diagnosis and treatment. All endoscopic procedures were carried out by a therapeutic-type video colonoscope (PCF-Q260AZI or CF-HQ290L/I; Olympus Medical Systems, Tokyo, Japan) with a video endoscopy system (EVIS LUCERA ELITE; Olympus Medical Systems). Video colonoscope insertion and endoscopic resection were carried out with a CO_2 insufflation regulation unit (UCR CO2 Regulation Unit; Olympus Medical Systems) in all patients. All the lesions diagnosed as SSA/P by M-NBI were treated by endoscopic mucosal resection (EMR), polypectomy, cold polypectomy, or underwater EMR. EMR, polypectomy and underwater EMR were performed using a bipolar snare (DRAGONARE™; Xemex, Tokyo, Japan). Cold snare polypectomy was mainly performed with a Profile snare (Boston Scientific, Marlborough, MA, USA).

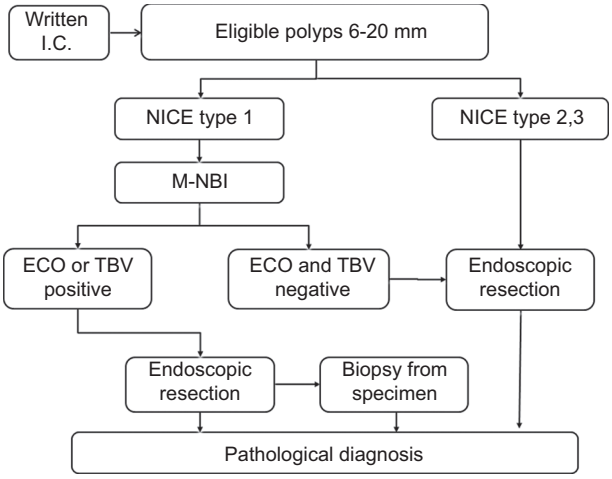

Figure 1 Diagnostic flow chart of this study
I.C., informed consent; M-NBI, magnifying narrow-band imaging; NICE, NBI International Colorectal Endoscopic Classification; ECO, expanded crypt opening; TBV, thick and branched vessel

After resection, the specimens were retrieved and one biopsy specimen was removed by the same endoscopist from the center of the resected lesions using biopsy forceps (Radial Jaw4 Standard Capacity; Boston Scientific, Marlborough, MA). The specimens were promptly immersed in 10% formalin and sent to the Department of Pathology.

Endoscopic diagnosis of SSA/P by M-NBI

When polyps were detected during colonoscopy, the endoscopists first observed them with non-magnifying NBI. The diagnostic criteria for non-magnifying NBI of SSA/Ps were those of NICE Type 1 [16]. If the NICE Type 1 criteria were met, the next step was to perform M-NBI. When expanded crypt openings (ECOs) and/or thick and branched vessels (TBVs) were seen under M-NBI, the endoscopists diagnosed SSA/Ps and performed endoscopic resection at the next colonoscopy. ECOs (Fig. 2A) and TBVs (Fig. 2B) are characteristic of M-NBI observation of SSA/Ps,and we previously reported that these findings have high sensitivity for the diagnosis of SSA/Ps [4].

Histopathological diagnosis of SSA/Ps

Histopathological diagnosis of biopsy and endoscopic resection specimens was made according to the criteria for SSA/Ps that have been established by the Japanese Society for Cancer of the Colon and Rectum [9,17]. These criteria comprise 3 pathological features: crypt dilation, irregularly branching crypts, and horizontally arranged basal area crypts (inverted T- and/or L-shaped crypts). If a serrated lesion has more than 2 of these features in more than 10% of the lesion, it can be diagnosed as SSA/P. The histological diagnosis was made by 2 pathologists blind to the endoscopic diagnosis, and the biopsy specimen removed from the EMR or polypectomy specimen was also

blinded. The pathological diagnosis of the endoscopic resection specimen was considered the conclusive diagnosis. The difference in diagnosis between the 2 pathologists was settled by discussion.

Study outcomes

The primary outcome was the diagnostic accuracy of endoscopy and biopsy. The diagnostic sensitivity, specificity and accuracy were calculated using the following formula: sensitivity = correctly diagnosed SSA/Ps/total SSA/Ps; specificity = correctly diagnosed non-SSA/Ps/total non-SSA/Ps; and accuracy = correctly diagnosed lesions/total lesions.

Sample size

In a previous report, the accuracy of endoscopy for SSA/P using non-magnifying NBI and M-NBI was reported to be about 85% [4,18]. We assumed that the accuracy of the pathological diagnosis would be about 60%, based on our previous report [19]. We estimated that 39 lesions in each group would be required to detect a significant difference between the groups with a significance level of 0.05 (1-sided) and a power of 80%.

Statistical analysis

The statistical significance of differences between endoscopic and histological biopsy diagnoses was determined by the McNemar test. Odds ratios were calculated using logistic regression models. P<0.05 (2-sided) was considered significant. All statistical analyses were carried out using SPSS statistics version 23 (IBM Corp., Armonk, NY, USA).

Results

Between August 2015 and October 2017, 6 expert endoscopists participated in this study and 295 lesions were resected by polypectomy or EMR. Of these, 97 polyps were classified as NICE type 1 and 198 as NICE type 2. Eighteen of the NICE type 1 polyps were negative for ECO and TBV using NBI magnification. Seventy-nine endoscopically resected specimens, endoscopically diagnosed as SSA/P underwent biopsy for histological examination (Fig. 3). However, 2 lesions were excluded because the specimens were too small for histological examination. Finally, 77 endoscopically resected specimens (64 resected by EMR, 6 by cold polypectomy, 4 by polypectomy, and 3 by underwater EMR) and 77 biopsy specimens in 64 patients were assessed histopathologically. The baseline characteristics are presented in Table 1. The patients comprised 29 men and 33 women with a median age (range) of 68 (38-87) years. The median resected lesion size (range) was 12 (6-23) mm. Histopathological examination showed 67 SSA/Ps, 8 HPs, and 2 adenomas. There were 3 SSA/Ps among the 216 lesions classified as NICE Type 2 or 3, or ECO and TBV negative. The sensitivity, specificity and accuracy of endoscopic M-NBI diagnosis of SSA/Ps were 95.7%, 95.5% and 95.6%, respectively. The sensitivity, specificity and accuracy of histological diagnosis of a single biopsy specimen were 71.6%, 90.0% and 74.0%, respectively (Table 2). Of the 22 cases diagnosed as HP by biopsy, 17 (77.2%) were diagnosed as SSA/P by pathology after endoscopic resection (Fig. 4).

The McNemar test was performed in 77 cases for which endoscopic and biopsy diagnoses were obtained and showed a significant difference between biopsy and endoscopic diagnoses (P [McNemar test] = 0.001; odds ratio 19.0, 95% confidence interval 3.0-789.5).

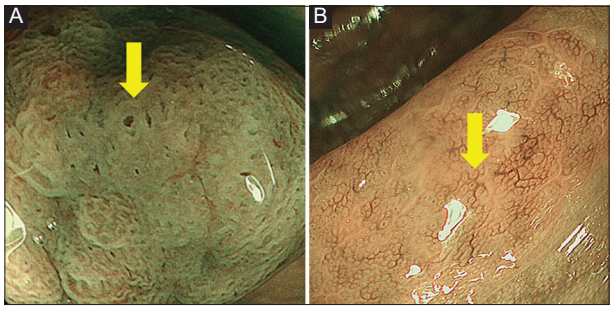

Figure 2 Magnifying narrow-band imaging showing polyp with expanded crypt opening (A: yellow arrow) and thick and branched vessels (B: yellow arrow)

Table 1 Baseline characteristics of patients and lesions

Characteristics	Value
Number of patients/polyps	64/77
Male/female	29/33
Age (years, median)	68 (38-87)
Polyp location (n)	
Cecum	12
Ascending colon	30
Transverse colon	18
Descending colon	8
Sigmoid colon	6
Rectum	3
Polyp size (mm, median)	12 (6-23)
Morphology (n)	
Is	17
Isp	2
IIa	58
Resection method (n)	
EMR	64
Cold polypectomy	6
Polypectomy	4
Underwater EMR	3
Pathological diagnosis of resected polyps (n)	
SSA/P	67
HP	8
Adenoma	2

EMR, endoscopic mucosal resection; SSA/P, sessile serrated adenoma/polyp; HP, hyperplastic polyp

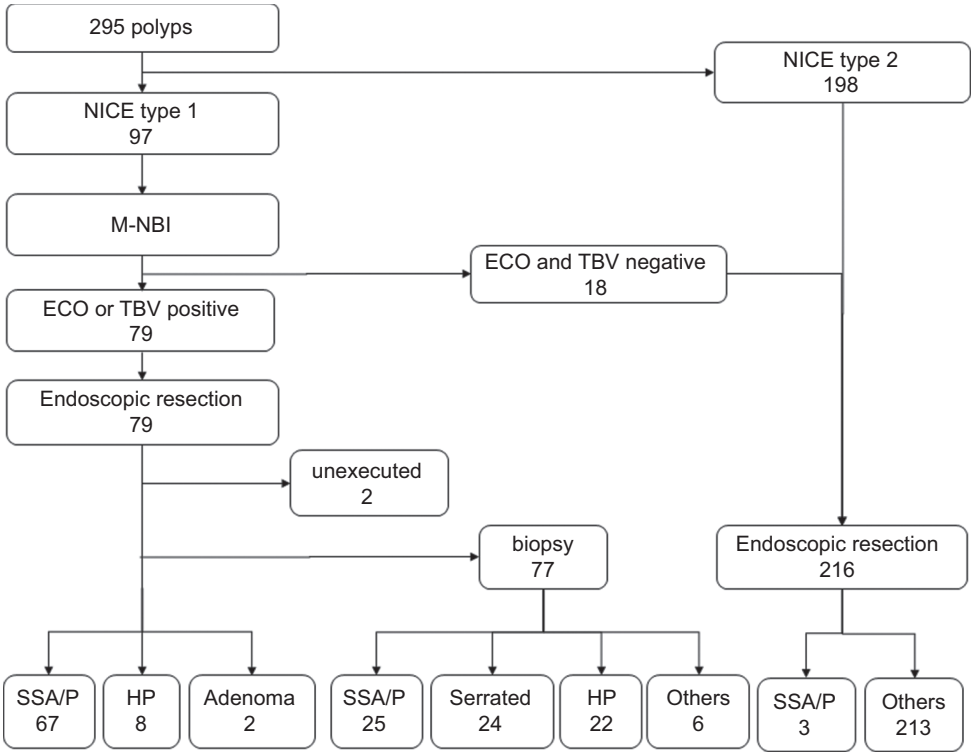

Figure 3 Flow chart of this study
M-NBI, magnifying narrow-band imaging; NICE, NBI International Colorectal Endoscopic Classification; ECO, expanded crypt opening; TBV, thick and branched vessel; SSA/P, sessile serrated adenoma/polyp; HP, hyperplastic polyp

Table 2 Sensitivity, specificity and diagnostic accuracy of biopsy and M-NBI

Parameter	Biopsy diagnosis	M-NBI diagnosis
Sensitivity (number) [95%CI]	71.6% (48/67) [59.3-82]	95.7% (67/70) [88.0-99.1]
Specificity (number) [95%CI]	90.0% (9/10) [24.4-71.1]	95.5% (213/223) [91.9-97.8]
Accuracy (number) [95%CI]	74.0 (57/77) [62.8-83.4]	95.6 (280/293) [92.5-97.6]

M-NBI, magnifying narrow-band imaging; CI, confidence interval

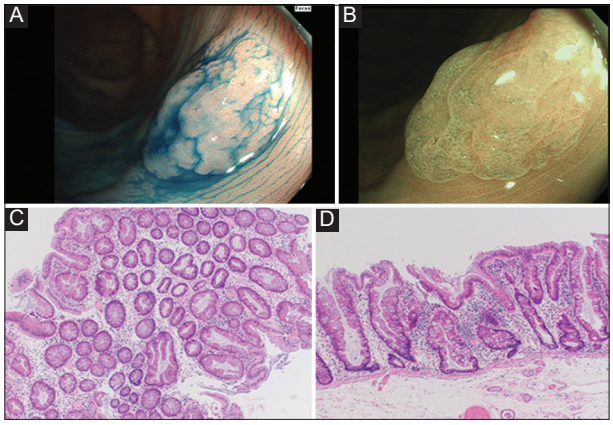

Figure 4 (A) White light endoscopy and (B) narrow-band imaging, showing polyp 15 mm in diameter with expanded crypt opening and thickened and branched vessels in the ascending colon. (C) Histological diagnosis of a single biopsy specimen was hyperplastic polyp. (D) Histologic diagnosis of a resected specimen was sessile serrated adenoma/polyp

Discussion

In this prospective study, we demonstrated that M-NBI for SSA/Ps had sensitivity, specificity and accuracy of 95.7%, 95.5% and 95.6%, which was a better diagnostic performance than that of biopsy. However, since biopsy was performed only for polyps suspected of being SSA based on M-NBI, it was not possible to directly compare the accuracy of diagnosis between M-NBI and biopsy. Therefore, we adopted the McNemar test, a non-parametric test used for the analysis of paired nominal data. The McNemar test also showed a significant difference between the results of the biopsy and endoscopic diagnoses.

To the best of our knowledge, there have been no studies comparing endoscopic and biopsy diagnoses, and this is the first study to compare M-NBI and biopsy diagnosis of SSA/Ps. Until recently, pathological diagnosis was the gold standard and the resolution of endoscopic imaging was low. The endoscopic diagnostic capability has also advanced remarkably in recent years. Nagai *et al* [20] compared the diagnostic accuracy of

endoscopy with M-NBI and biopsy for esophageal squamous lesions and demonstrated the non-inferiority of the endoscopic diagnosis. Their finding suggests the practicality of endoscopic optical diagnosis. We also believe that endoscopic diagnosis will be considered a sufficient substitute for biopsy diagnosis of SSA/Ps in the future.

Recently, SSA/Ps have attracted attention as precancerous lesions that need to be treated differently from HPs, which have a low risk of canceration. Additionally, SSA/Ps are said to be a cause of interval cancer [21,22], and if SSA/Ps are diagnosed as HPs by biopsy alone and followed up, they may progress to interval cancer. In this study, we used ECOs and TBVs for the diagnosis of SSA/Ps. Several other reliable diagnostic criteria have been reported to distinguish SSA/Ps from HPs, such as thickened and dilated vessels, and expanded and dilated crypt openings [23,24]. A reliable diagnosis for SSA/P using these criteria is important and may lead to subsequent treatment and prevention of interval cancer.

Diagnostic features of SSA/Ps can mainly be detected around the colon crypt bases: e.g., serrated architecture begins in the deep basal regions of the crypts and inverted T- and/or L-shaped crypts are horizontally arranged basal area crypts [1,7-11]. We believe that it may be difficult to obtain tissue around the colon crypt bases, characteristic of SSA/Ps, because biopsies are taken from the surface of the colonic mucosa. Furthermore, if the biopsy section is not cut vertical to the crypt, the area around the colon crypt base may not be included and pathological diagnosis may also be difficult. In contrast, endoscopic diagnosis may be able to capture the features of colon crypt bases. Kimura *et al* reported the typical findings of SSA/Ps as a type II-O pit pattern [25]. This pattern is thought to correspond to histopathologically dilated crypt openings, a typical histopathological feature of SSA/Ps. Similarly, M-NBI is thought to capture the features of SSA/Ps around the colon crypt bases [4,6,18].

Endoscopic diagnosis has other advantages over pathological diagnosis. One is that the pathological diagnosis is costly. Kessler *et al* stated that removing the need for histological evaluation of resected diminutive polyps can provide significant cost savings [12]. They showed that endoscopic diagnosis of polyps during colonoscopy and subsequent pathological examination could result in substantial up-front cost savings. Also, from the viewpoint of differentiating between SSA/Ps and HPs, histopathology for these multiple diminutive polyps, sometimes suspected as HPs, is costly. Furthermore, most of these are actually HPs and do not need to be resected, so endoscopic diagnosis can be cost-effective. We also believe that endoscopic diagnosis is cost-effective in terms of differentiating SSA/Ps from HPs. This is because we often encounter multiple diminutive polyps suspicious for HPs, and the pathological diagnosis of these polyps is costly.

It has been pointed out that biopsies may cause delayed bleeding after the procedure [15], although this is rare. However, serious delayed bleeding may require endoscopic treatment, blood transfusion, or hospitalization. Biopsies may also cause fibrosis, leading to poor lifting of the submucosa, which may make subsequent endoscopic resection difficult [13,14]. For endoscopic diagnosis, just simply changing to NBI mode has the advantage of no complications and lower costs.

Our study had some limitations. First, biopsies were performed on polyps larger than 6 mm, and hence so-called diminutive polyps were excluded. There was a possibility that some SSA/Ps may have been present in the excluded polyps of ≤5 mm, which may have affected the diagnostic performance. However, according to Ponugoti *et al*, SSA/Ps are rarely found in diminutive polyps [26] and follow up is acceptable; therefore, it is likely that this had little impact on our results. Second, the biopsies were taken from post-EMR specimens, which may be different from biopsies in routine clinical practice. However, because the biopsies were taken from the center of the specimens immediately after resection, there was little tissue damage, and we believe this is almost identical to routine clinical practice. Additionally, the pathological results showed that only 4 cases of non-tumor mucosa were found; therefore, we believe that the sampling site was appropriate. In addition, all the resected specimens underwent proper pathological evaluation, and we believe that the biopsy did not cause any damage to the resected specimens. Third, not all patients were enrolled, and more patients with suspected SSA/P may have been enrolled. In fact, as the lesions enrolled in this study were larger in size, more often located in the right colon, and flatter in morphology, it was possible that the population had a high prevalence of SSA/Ps. Therefore, as reported by Usher-Smith *et al*, the sensitivity may be reduced if our results are applied to general clinical practice [27]. It would be desirable to study this issue in a multicenter study with a variety of patients.

In conclusion, this study shows that M-NBI may be useful for the endoscopic diagnosis of SSA/Ps in a daily clinical setting, and that biopsy may be avoided by using M-NBI in patients with suspected SSA/Ps. Further study in a multicenter setting is warranted in the future.

Acknowledgment

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Summary Box

What is already known:

- Magnifying narrow-band imaging (M-NBI) has high accuracy in the endoscopic diagnosis of sessile serrated adenoma/polyps (SSA/Ps)
- The diagnostic accuracy of biopsy for SSA/Ps is unclear

What the new findings are:

- The endoscopic diagnosis for SSA resulted in a higher diagnostic accuracy than the biopsy diagnosis
- Biopsy may be avoided by using M-NBI in patients with suspected SSA/Ps

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