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The Natural History of Non-Polypoid Colorectal Neoplasms

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KEYWORDS

• Non-polypoid colorectal neoplasms • Depressed lesion
• De novo cancer • Colonoscopy • Natural history

The importance of non-polypoid colorectal neoplasms (NP-CRN) is now recognized throughout the world.[1–9] There is little information, however, known about the natural history of NP-CRN, perhaps because the initial reports of NP-CRN suggested that it had high risk of invasion and lymph node metastasis as compared with polypoid lesions of similar size.[10,11] Long-term follow-up of NP-CRN without resection was therefore not an accepted treatment strategy, and had been reported only based on analysis of interval neoplasms or sporadic case reports. In addition, outside Japan, many endoscopists viewed NP-CRN, especially the depressed lesion, as a uniquely Japanese phenomenon and thus, paid little attention to such lesions, limiting the data even more. This article will summarize the available data to gain some estimates of the natural history of NP-CRN.

RADIOGRAPHIC ANALYSIS

Matsui and colleagues[12] reported a retrospective analysis of a series of colorectal cancers that were missed by double-contrast barium enema examinations. They found six depressed and seven flat lesions (41%) could be retrospectively identified as antecedent lesions that gave rise to 32 advanced cancers. The authors found that all depressed lesions developed into nonprotuberant-type advanced colorectal cancers, whereas flat or polypoid lesions had a possibility to develop into either protuberant or nonprotuberant-type advanced colorectal cancers.

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Umetani and colleagues[13] reported 11 cases of colorectal cancers that had more than two barium enema examinations that were at least 6 months apart. Five non-polypoid submucosal invasive cancers were studied; three developed from non-polypoid and two from polypoid lesions. The authors estimated tumor doubling time to evaluate the growth rate of each tumor, and suggested that NP-CRN grew slowly compared with polypoid lesion and maintained their macroscopic morphology. The data, however, are limited.

COLONOSCOPIC ANALYSIS

Matsui and colleagues[14] reported eight early colorectal cancers that were incidentally followed by colonoscopy. Thirty-five cases, including 14 NP-CRN as initial lesions, were reviewed. They found that NP-CRN progressed to submucosally invasive cancer, retaining its non-polypoid configuration, and some flat lesions developed depressed areas during their progression. Although the authors also estimated the speed of growth compared with polypoid and non-polypoid lesions, they could not conclude which type grew more rapidly.

Sato and colleagues[15] prospectively followed 12 small flat adenomas. The size of the lesions ranged from 2 to 6 mm (median 4 mm), and the observation period ranged from 11 to 26 months (median 19 months). Although eight lesions showed various changes in their shape, only two lesions demonstrated an increase in diameter of the tumor. All of the flat lesions were subsequently removed endoscopically and found to be adenomas. The authors concluded small flat adenoma did not rapidly progress, and configuration change did not indicate tumor progression or invasion.

Watari and colleagues[16] conducted prospective colonoscopic study to elucidate the natural history of NP-CRN. The authors observed 75 colorectal tumors measuring less than 1 cm in diameter in 50 patients. The average follow-up period was 22 months, and 62 lesions (83%) were NP-CRN. They concluded similar observations as those of Sato and colleagues, although they found that 40% of small non-polypoid lesions had exophytic growth with time. This finding suggested some small non-polypoid lesions follow the adenoma–carcinoma sequence the same as polypoid lesions.

THE IMPORTANCE OF THE DEPRESSED-TYPE NP-CRN

Matsuda and colleagues[17] analyzed 6638 colorectal neoplasms, excluding advanced cancers, treated in National Cancer Center Hospital, Tokyo, Japan. There were 4471 (67%) and 2167 (33%), polypoid and non-polypoid colorectal neoplasms, respectively. Among all non-polypoid lesions, there were 178 (2.7%) depressed lesions, 109 (61%) of which were diagnosed as high-grade dysplasia or submucosally invasive cancer. Among 5538 (83%) lesions that were identified as low- or high-grade dysplasia, the proportion of depressed lesions was 1.3%. On the other hand, depressed type was identified in 39% (**Table 1**) of submucosal cancers. This discrepancy may indicate of a rapid progression rate of depressed lesions into invasive cancers.

Sano and colleagues[18] described the incidence of depressed lesions among all of colorectal neoplasms, again excluding advanced cancers. Their multicenter retrospective study conducted in eight Japanese referral institutes revealed that the incidence of depressed lesions was 1.94% (1291 depressed lesions out of 66,670 neoplasms), and, in particular, 51.2% of intramucosal depressed lesions were diagnosed as high-grade dysplasia. These data also suggested that intramucosal depressed lesions showed more aggressive behavior and were perhaps more likely

Table 1
Relationship between macroscopic type and histopathological findings

	LGD	HGD	SM-Ca
Polypoid	3781 (68.3)	578 (67.9)	112 (45.0)
Flat	1688 (30.5)	260 (30.6)	41 (16.5)
Depressed	69 (1.2)	13 (1.5)	96 (38.6)
Total	5538 (83.4)	851 (12.8)	249 (3.8)

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia; SM-Ca, submucosal invasive cancer.

Data from Matsuda T, Saito Y, Hotta K, et al. Prevalence and clinicopathological features of non-polypoid colorectal neoplasms: should we pay more attention to identifying flat and depressed lesions? Dig Endosc 2010;22(Suppl 1):S57–62.

to develop into invasive cancers as compared with the polypoid lesions. The depressed type of NP-CRN appears to be pathologically and molecular biologically distinct that other types of NP-CRN.

Several authors reported that depressed-type colorectal cancer does not arise from an adenomatous polyp. This theory was called de novo carcinogenesis, and lack of K-ras mutation was thought to be a distinctive genetic feature.[10,11,19,20] Goto and colleagues[21] reported the proportion of de novo cancers among all colorectal cancers in a cohort of 14,817 Japanese populations. The authors defined de novo cancers according to both criteria: (1) the absence of adenomatous components and (2) all lateral margins of the tumor covered with normal mucosa and non-polypoid growth pattern. They concluded that 22.9% of early colorectal cancers were de novo cancers. Chen and colleagues,[22] from Taiwan, also assessed the proportion of de novo carcinomas using the Markov model, and demonstrated about 30% of colorectal cancers arising from de novo sequence.

Table 2
Description of 13 interval cancers diagnosed within 3 years of a initial colonoscopy

Number	Macroscopic Type	Size (mm)	Location	Depth of Lesion
1	Isp (semipedunculated)	13	Sigmoid	SM
2	Isp (semipedunculated)	15	Sigmoid	SM
3	Is (sessile)	8	Rectum	SM
4	Is (sessile)	10	Sigmoid	SM
5	Is (sessile)	20	Rectum	MP
6	Is (sessile)	6	Transverse	SM
7	IIa (flat)	15	Transverse	SM
8	IIa (flat)	20	Sigmoid	SM
9	IIa + IIc (depressed)	20	Cecum	SM
10	IIa + IIc (depressed)	20	Transverse	SM
11	IIa + IIc (depressed)	10	Rectum	MP
12	IIa + IIc (depressed)	6	Ascending	SM
13	IIa + IIc (depressed)	20	Sigmoid	SS

Abbreviations: MP, muscularis; SM, submucosa; SS, subserosa.

Data from Matsuda T, Fujii T, Sano Y, et al. Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol 2009;39:435–42.

THE JAPAN POLYP STUDY

To clarify the natural history of NP-CRN, a large cohort study focused on the detection of NP-CRN is required. Matsuda and colleagues[23] reported the results of multicenter retrospective cohort study to evaluate 5-year incidence of advanced neoplasia after initial colonoscopy. The authors studied 5309 patients with a median follow-up period of 5.1 years. Endoscopists diagnosed 13 invasive cancers on follow-up within 3 years. The initial colonoscopies were performed by Japanese endoscopists who had proficient technique with chromoendoscopy to diagnose NP-CRN, and the patients had good preparation quality, taking polyethylene glycol (PEG) solution in the morning on the day of colonoscopy, Out of the 13 incident cancer cases, seven were NP-CRN, and the mean size of these lesions was less than 15 mm in diameter (**Table 2**). These data suggested that NP-CRN is responsible for interval cancers, defined as colorectal cancers diagnosed within several years of a complete colonoscopy. Much prospective data, however, are necessary to elucidate the natural history and epidemiology of these lesions. The Japan Polyp Study (JPS) is a multicenter randomized controlled trial prospectively evaluating follow-up surveillance strategy for Japanese patients after removal of all polypoid and non-polypoid neoplasms.[24] This study is intended to continue until 2011 and hopefully will provide new information on the detection and progression of NP-CRN.

SUMMARY

The natural history of NP-CRN is mostly unknown. The results of small observational studies suggest that NP-CRN lesions develop into invasive cancer with minimal size expansion. Among NP-CRN lesions, depressed lesions show more aggressive behavior and frequently develop into invasive cancers compared with polypoid lesions, regardless of their low incidence. A large prospective cohort study focused on the detection of NP-CRN is currently ongoing.

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Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program

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Background: Previous reports assessing diagnostic skill using narrow-band imaging (NBI) and pit pattern analysis for colorectal polyps involved only highly experienced endoscopists.

Objective: To evaluate diagnostic skills of less-experienced endoscopists (LEE group) for differentiation of diminutive colorectal polyps by using NBI and pit pattern analysis with and without magnification after an expanded training program.

Design: Prospective study.

Patients: This study involved 32 patients with 44 colorectal polyps (27 adenomas and 17 hyperplastic polyps) of ≤5 mm that were identified and analyzed by using conventional colonoscopy as well as non-magnification and magnification NBI and chromoendoscopy followed by endoscopic removal for histopathological analysis.

Intervention: Before a training course, 220 endoscopic images were distributed in randomized order to residents with no prior endoscopy experience (NEE group) and to the LEE group, who had performed colonoscopies for more than 5 years but had never used NBI. The 220 images were also distributed to highly experienced endoscopists (HEE group) who had routinely used NBI for more than 5 years. The images were distributed to the NEE and LEE groups again after a training class. Magnification NBI and chromoendoscopy images were assessed by using the Sano and Kudo classification systems, respectively.

Main Outcome Measurements: Diagnostic accuracy and interobserver agreement for each endoscopic modality in each group.

Results: Diagnostic accuracy was significantly higher, and kappa (κ) values improved in the LEE group for NBI with high magnification after expanded training. Diagnostic accuracy and κ values when using high-magnification NBI were highest among endoscopic techniques for the LEE group after such training and the HEE group (accuracy 90% vs 93%; κ = 0.79 vs 0.85, respectively).

Limitations: Study involved only polyps of ≤5 mm.

Conclusion: Using high-magnification NBI increased the differential diagnostic skill of the LEE group after expanded training so that it was equivalent to that of the HEE group. (Gastrointest Endosc 2010;72:127-35.)

Abbreviations: CC, conventional colonoscopy; CE-H, high-magnification chromoendoscopy; CE-L, low-magnification chromoendoscopy; HEE, highly experienced endoscopist; LEE, less-experienced endoscopist; NBI, narrow-band imaging; NBI-H, high-magnification narrow-band imaging; NBI-L, low-magnification narrow-band imaging; NEE, no-experience endoscopist; SSA, sessile serrated adenoma.

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It is widely accepted that adenomatous polyps are precursors of colorectal cancer, and performing polypectomies on such lesions can reduce the risk of subsequent colorectal cancer by up to 80% for a period that may exceed 10 years.[1] In addition, adenomas are a major factor in guidelines that have been developed for recommended colonoscopy surveillance intervals after polypectomies because they are a powerful predictor for future colorectal cancer risk.[1-3] Small colorectal adenomas as well as advanced adenomas[4] are precursors of colorectal cancer, and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[5]

Endoscopic differentiation of small adenomas from non-adenomatous polyps is important because endoscopists should avoid performing any unnecessary procedure, including polypectomies, that can cause related complications such as bleeding and perforation.[6,7] The diagnostic accuracy of conventional colonoscopy for such colorectal polyps, however, has previously been reported to be unsatisfactory.[8,9] In contrast, chromoendoscopy with indigocarmine dye spraying has been shown to be an effective procedure for detecting and evaluating colorectal polyps[10-15] despite having several disadvantages, including a longer procedure time and the additional cost for dye spraying.

Narrow-band imaging (NBI) is an innovative optical technology providing a unique image that emphasizes the morphological and structural character of lesions as well as their surface capillary patterns.[16-25] It has been reported that this modality is a new non-dye tool for differentiating neoplastic from non-neoplastic polyps, with a diagnostic accuracy including pit pattern analysis equivalent to that of chromoendoscopy.[17-21] Such reports have been based on studies involving only highly experienced endoscopists, however, with few published articles concerned with the learning curve for NBI being dependent on an individual endoscopist's experience and ability. The aim of this study was to determine, therefore, whether expanded training in the effective use of NBI and pit pattern analysis with and without magnification would improve the diagnostic skill of less-experienced endoscopists in the differentiation of diminutive colorectal polyps.

Take-home Message

- Expanded interactive training in effective use of narrow-band imaging both with and without magnification as well as pit pattern analysis improved diagnostic accuracy and interobserver agreement of less-experienced colonoscopists in differentiating diminutive colorectal polyps. Using narrow-band imaging with high magnification increased the differential diagnostic skill of less-experienced colonoscopists who underwent such training to a level equivalent to that of highly experienced colonoscopists.

METHODS

Patients

Patients scheduled for a total colonoscopy at Okayama University Hospital and Sumitomo Besshi Hospital between September and October 2008 were invited to participate in this study. Informed consent was obtained from all patients before their examinations. Patients with inflammatory bowel disease, familial adenomatous polyposis, an international normalized ratio greater than 2.0, or a platelet count less than 50,000/mm^3 were excluded from this study.

Colonoscopy and polyp assessment protocol

Bowel preparation consisted of patients drinking 2 to 3 liters of polyethylene glycol solution in the morning before their procedures.[13] Total colonoscopies were prospectively performed by using a video endoscopic system (EVIS, Lucera Spectrum; Olympus Co, Tokyo, Japan) with CF-H260AZI or PCF-Q240ZI magnification colonoscopes (Olympus) by two highly experienced endoscopists (R.H., T.U.), each of whom had previously performed over 1000 colonoscopies annually.

When a lesion was detected by conventional colonoscopy examination, surface mucus was washed away with lukewarm water, and endoscopic images were taken in the following order: conventional colonoscopy (CC), low-magnification NBI (NBI-L), high-magnification NBI (NBI-H), low-magnification chromoendoscopy (CE-L) and high-magnification chromoendoscopy (CE-H). A standard optical filter was used for both CC and chromoendoscopy, with chromoendoscopic images taken after 0.2% indigocarmine dye was sprayed on the lesion surface. The enhanced surface structure function of the video image processor at the level A5 setting was used in taking all endoscopic images.[23] Location, size, and macroscopic type of each lesion were recorded, with size measured by using open forceps. Lesions were classified macroscopically based on the criteria of the Paris classification of superficial GI lesions.[26] A biopsy, polypectomy, or EMR was then performed, and the resulting specimen was analyzed histopathologically.

Image evaluator categories

A total of 12 doctors with different levels of endoscopic experience were asked to independently evaluate endoscopic images. The doctors were separated into 3 groups: 4 residents with no prior endoscopy experience (NEE group); 4 less experienced endoscopists each of whom had performed colonoscopies for more than 5 years but had never used NBI (LEE group); and 4 highly experienced endoscopists each of whom had routinely used magnification colonoscopy with NBI for more than 5 years (HEE group).

Assessment of endoscopic images

The best quality endoscopic images were selected for each modality and stored digitally in JPEG format. All images were distributed in randomized order to each group of evaluators. For the NEE and LEE groups, the same images were distributed in randomized order once before and once after those group members participated in an intensive, 1-hour, interactive training program on white-light endoscopy, NBI, and chromoendoscopy. The program included information on the Sano NBI classification[20,21] and the Kudo pit pattern classification[27,28] and used an atlas of endoscopic images of polyps produced by an independent group of highly experienced endoscopists. Although they were completely unaware of the histopathological results, every participant correctly diagnosed polyps as either neoplasms or non-neoplasms by using (1) chromoendoscopy based on the Kudo pit pattern classification, with types III (including IIIL and IIIs), IV, and V (including VI and VN) considered to be neoplasms and types I and II regarded as non-neoplasms;[27,28] (2) NBI-L that revealed a brownish area determined to be neoplastic; and (3) NBI-H with the Sano classification of meshed capillary vessel pattern, in which types II and III were considered neoplastic and type I, without meshed capillaries, was non-neoplastic (Figs. 1 and 2).[20-21] Patient information such as age, sex, and clinical diagnosis was not disclosed to any of the evaluators, and discussions were not permitted among the doctors individually or in groups.

Statistical analysis

The diagnostic accuracy of each endoscopic modality was assessed in reference to histopathological results. Estimates of diagnostic accuracy were calculated based on the average diagnostic accuracy for each group of doctors as well as for each diagnostic modality. The upper and lower 95% confidence interval (CI) limits were calculated by using a normal model that consisted of symmetric CIs, with limits at a distance from the estimate equal to the product of 1.96 times the standard error. Interobserver agreement in diagnosing colorectal lesions in each group and by each modality was determined by calculation of the kappa statistic (κ) and its 95% CI by using the Fleiss method. Diagnostic accuracies before training and after training in the NEE and LEE groups were compared with the McNemar test. As for differences in diagnostic accuracies after training among the NEE, LEE, and HEE groups, those findings were analyzed by using the Fisher exact test. Multiple statistical testing of outcome data was conducted in this study, therefore, a Bonferroni correction was applied, and differences with a P value of $< .025$ were considered significant as the correction. A κ value of <0.4 was regarded as poor agreement, 0.41 to 0.60 fair agreement, 0.61 to 0.80 good agreement, and >0.80 excellent agreement. Statistical analyses were conducted by using version 7.0 of the JMP statistical software package (SAS Institute, Cary, NC) and a Microsoft Excel 2007 spreadsheet (Microsoft, Renton, Wash).

RESULTS

Clinicopathological features of colorectal lesions

Seventy-two consecutive patients were enrolled in this study for prospective endoscopic evaluation. A total of 44 lesions of ≤5 mm were identified and analyzed in 32 patients (Table 1). Mean (± standard deviation [SD]) patient age was 61.2 ± 12.3 years, and the male/female ratio was 2.2:1. Bowel preparation was considered adequate in all examinations, and complete colonoscopy was performed to the cecum in every case. There were no complications during any procedure. Of the 44 lesions, 37 were macroscopically classified as type 0-Is, 6 as type 0-IIa, and 1 as type 0-IIc. Mean (± SD) lesion size was 3.4 ± 1.1 mm. As for location, 22 polyps (50%) were found in the right colon (cecum, ascending, and transverse colon), 14 (32%) in the left colon (descending and sigmoid colon), and 8 (18%) in the rectum. Histopathological assessments included 27 adenomas (61%) and 17 hyperplasic polyps (39%). A total of 220 images of the 44 lesions were collected as each lesion was photographed during CC, NBI-L, NBI-H, CE-L, and CE-H.

Diagnostic accuracy of NBI and pit pattern analysis

Table 2 indicates diagnostic accuracy for each endoscopic modality. In the NEE group, diagnostic accuracies using CC, NBI-L, and NBI-H significantly improved after the training program (CC, $P < .001$; NBI-L, $P = .006$; and NBI-H, $P < .001$), but the NEE group's diagnostic accuracies were still significantly lower in all modalities except CC compared with the HEE group (CC, $P = .049$; NBI-L, $P = .0023$; NBI-H, $P < .001$; CE-L, $P < .001$; and CE-H, $P < .001$). Diagnostic accuracies in the LEE group for NBI-L, NBI-H, and CE-H also improved significantly after the training program ($P = .001$, $P < .001$, and $P = .001$, respectively). In contrast with the NEE group's results, however, subsequent diagnostic accuracies of the LEE group were not significantly different from diagnostic accuracies of the HEE group with respect to the CC, NBI-L, NBI-H, CE-L, and CE-H modalities ($P = 1.0$, $P = .60$, $P = .57$, $P = .031$, and $P = .48$, respectively).

Assessment of interobserver agreement based on endoscopic experience

Interobserver agreements in the HEE group for NBI-H were >0.80 representing excellent agreement and >0.60 for NBI-L, CE-L, and CE-H, representing good agreement (κ value CC, 0.5; NBI-L, 0.62; NBI-H, 0.85; CE-L, 0.69; CE-H

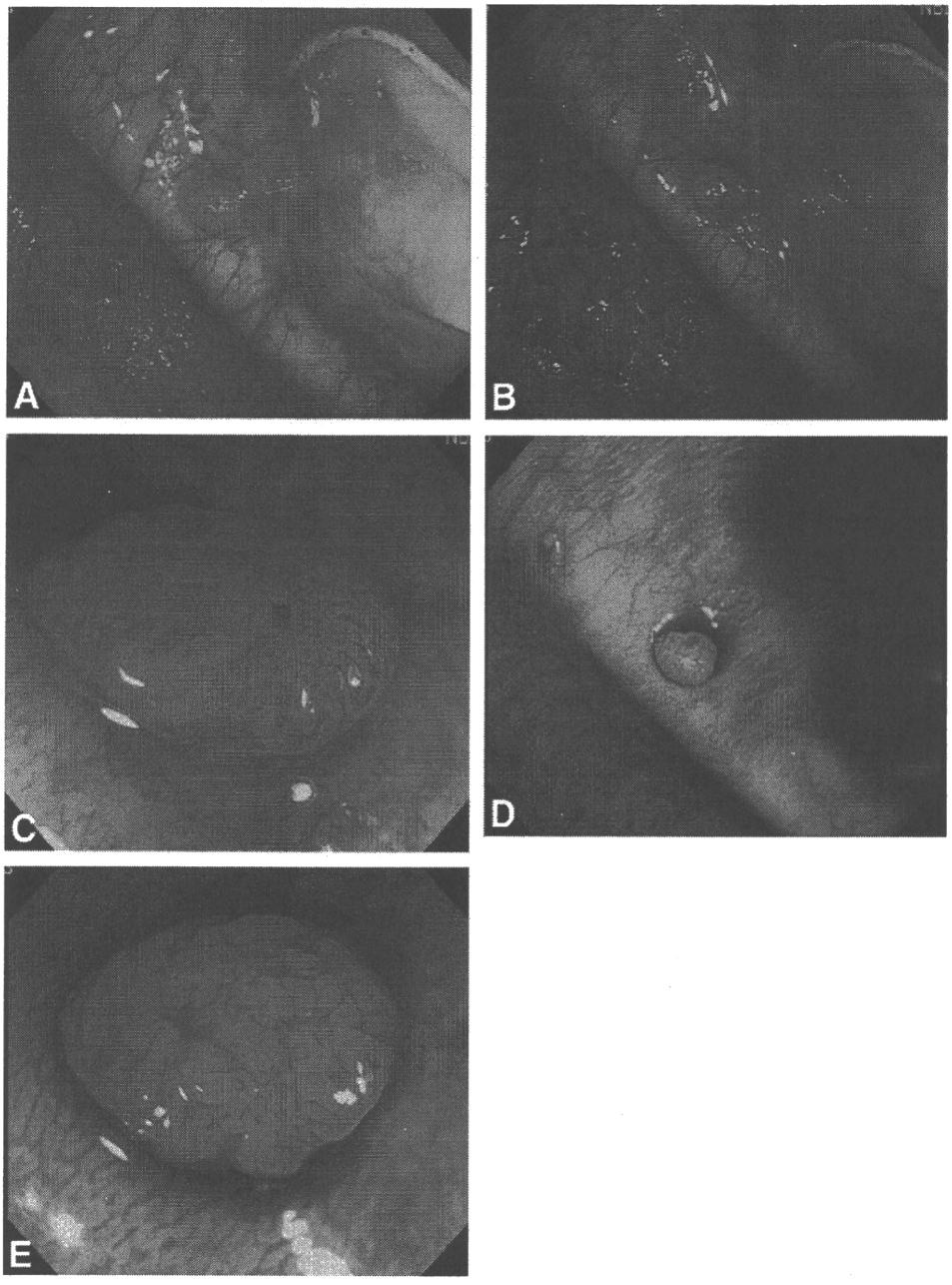

Figure 1. Examples of colorectal neoplastic polyps viewed by different endoscopic modalities in this study. **A,** Conventional colonoscopy view. **B,** Low-magnification NBI showed a brownish area. **C,** High-magnification NBI revealed meshed capillary vessels indicative of Sano classification type II. **D,** Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated margins and surface structure. **E,** High-magnification chromoendoscopy clearly indicated Kudo classification type IIIL. *NBI,* narrow-band imaging.

0.7). Meanwhile, κ values for NBI-H in the LEE group improved to "good agreement" after the training program, whereas the κ values for NBI-L, CE-L, and CE-H in the LEE group improved to "fair agreement" after the training program (κ value before vs after training: NBI-H, 0.46 vs 0.79; NBI-L, 0.31 vs 0.54; CE-L, 0.32 vs 0.44; and CE-H, 0.33 vs 0.59). In contrast, however, none of the κ values for any of the modalities in the NEE group improved beyond "poor agreement" after the training program (CC, -0.068 vs 0.24; NBI-L, 0.059 vs 0.25; NBI-H, 0.16 vs 0.39; CE-L, 0.28 vs 0.23; and CE-H, 0.12 vs 0.18) (Fig. 3).

When we compared diagnostic accuracy for each modality in the NEE group after the training program, the LEE group after the training program, and the HEE group, NBI-H had the highest accuracy rate among all 3 groups (Table 2). Similarly, the κ value for NBI-H was significantly higher in the NEE group after the training program, the LEE group after the training program, and the HEE group

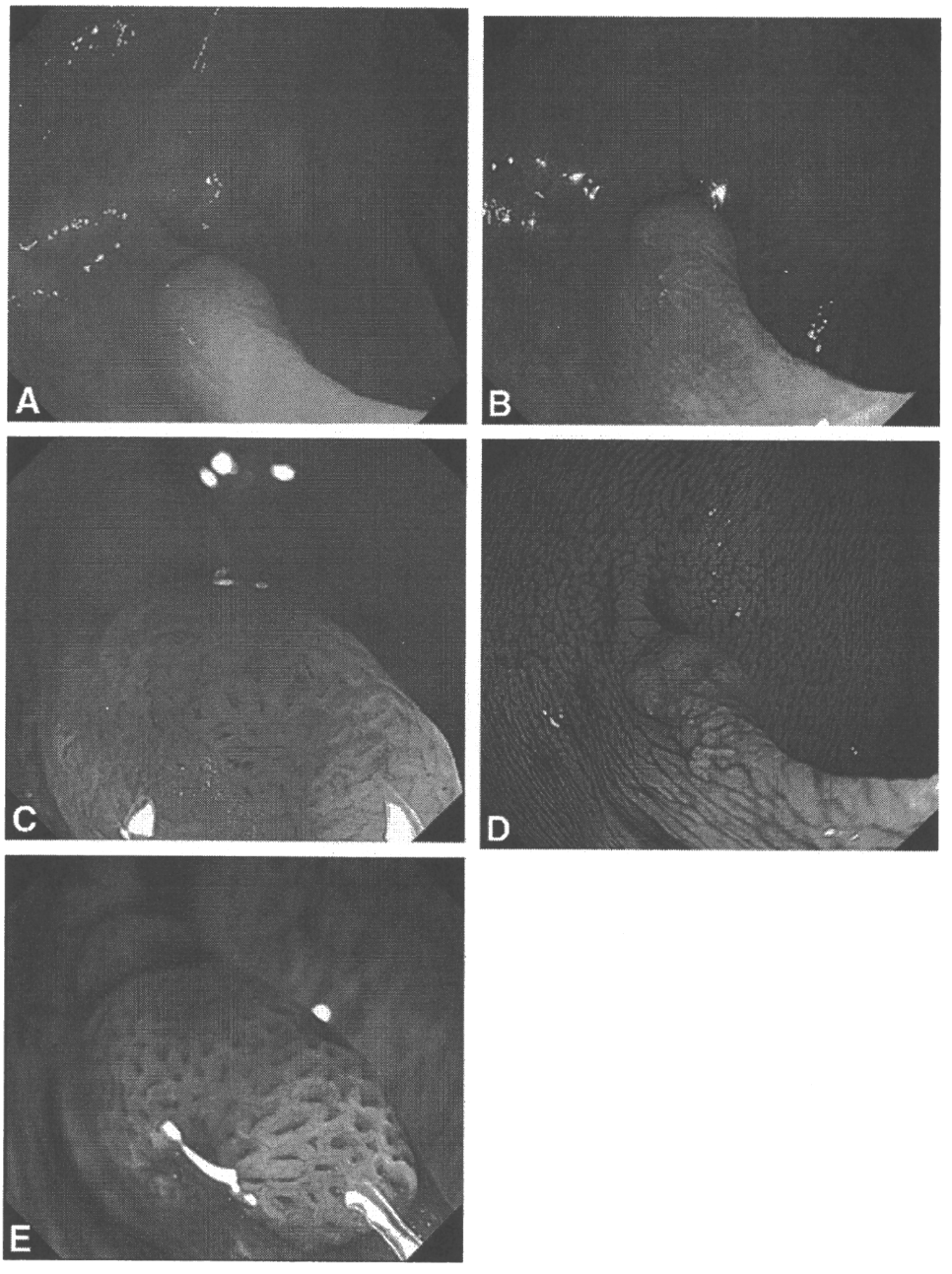

Figure 2. Examples of colorectal non-neoplastic polyps viewed by different endoscopic modalities in this study. **A,** Conventional colonoscopy view. **B,** Low-magnification NBI showed a non-brownish area. **C,** High-magnification NBI in which meshed capillary vessels were not visible or only faintly visible, indicative of Sano classification type I. **D,** Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated margins and surface structure. **E,** High-magnification chromoendoscopy clearly indicated Kudo classification type II. *NBI,* narrow-band imaging.

compared with the other endoscopic diagnostic modalities (Fig. 3).

DISCUSSION

Endoscopic diagnostic tools and technology are expected to be accurate and provide reliably reproducible agreement as well as be easy to use, readily available, and relatively inexpensive, but sufficient skill on the part of the endoscopist is still required for proper diagnosis. Our prospective study demonstrated significant improvement in the LEE group in diagnostic accuracy when using NBI and CE after undergoing limited but intensive training. The improved diagnostic accuracy of the LEE group was equivalent to that of the HEE group in terms of differential diagnosis using NBI-L, NBI-H, and CE-H. In addition, both higher diagnostic accuracy (>80%) and good interobserver agreement (κ value >0.6) for diminutive colorectal

TABLE 1. Patient characteristics and histopathological features of lesions

Patients (n = 32)	
Sex, male/female	22/10
Age, years, mean (± SD)	61.2 (12.3)
Lesions (n = 44)	
Macroscopic type	
0-Is	37
0-IIa	6
0-IIc	1
Size, mm, mean (± SD)	3.4 (1.1)
Location (right*/left†/rectum)	22/14/8
Histopathology	
Tubular adenoma	27
Hyperplastic polyp	17

SD, Standard deviation.
*Right: cecum, ascending colon, and transverse colon.
†Left: descending colon and sigmoid colon.

polyps were achieved by the LEE group when using NBI-H after the training program.

The fact that the diagnostic accuracy and κ value of NBI-H were the highest among all the endoscopic techniques analyzed in this study for both the NEE and LEE groups after the expanded training program as well as for the HEE group leads us to suggest that NBI-H is more accurate and provides a higher level of reproducible agreement than the other diagnostic tools in differentiating diminutive neoplastic from non-neoplastic colorectal polyps. Chiu et al[29] earlier validated that diagnostic accuracy of NBI-H was equivalent to that of CE-H. Their study reported that diagnostic accuracies for two experienced endoscopists ranged from 91% to 92% using CE-H and from 87% to 90% using NBI-H. In our study, the diagnostic accuracy of the HEE group was 85% (95% CI, 79%-89%) using CE-H and 93% (95% CI, 88%-96%) with NBI-H, although the difference between the accuracy of the two modalities was not significant. Earlier reports analyzing the diagnostic accuracy rate based on polyp size indicated that differentiation using CE-H was more difficult with diminutive colorectal polyps of <6 mm in size.[6-7]

Our results indicated that it was possible to significantly improve the diagnostic skill for differentiating diminutive colorectal polyps by using NBI-L, NBI-H, CE-L, and CE-H in the LEE group following the limited but intensive 1-hour interactive training program. We believe that, of the various endoscopic modalities, the use of NBI-H by the LEE group subsequently became both statistically equivalent to that of the HEE group in terms of diagnostic accuracy and closest to reaching "excellent agreement" compared with the other modalities in terms of κ value for two possible reasons. The first concerns the smaller size of the polyps examined in this study, because diagnostic accuracy of diminutive colorectal polyps by using CE-H has been reported to be lower than for polyps of >5 mm.[6-9] It is conceivable that differentiation of diminutive colorectal polyps could have been similarly affected, somehow reducing the diagnostic accuracy of CE-H while not affecting the diagnostic accuracy of NBI-H by the LEE group. Secondly, the possibility exists that members of the LEE group were able to recognize whether or not there were meshed capillary vessels on the surface of the mucosa easier than they could identify the pit patterns of diminutive colorectal polyps.

In the Rogart et al[30] report on the NBI learning curve, diagnostic accuracy by using NBI-L significantly improved as the experience level of endoscopists increased, with the diagnosis of approximately 130 lesions necessary for basic competency. Their findings indicated that educational sessions conducted before the assessment of lesions in combination with continual feedback regarding the accuracy of endoscopic diagnoses compared with histopathological results every 2 weeks for half a year were important factors in achieving a satisfactory learning curve. It has also been reported that use of the Kudo pit pattern classification required a longer learning curve, with experience from diagnosing at least 200 lesions needed to become competent.[6,7,31] In contrast, our study demonstrated that an expanded 1-hour intensive interactive training program conducted by a highly experienced endoscopist enabled the LEE group members in particular to accelerate their learning curve. In addition, the Sano classification with NBI-H appears to have had a shorter learning curve compared with using NBI-L or the Kudo pit pattern classification in the diagnostic differentiation of diminutive colorectal polyps.

Besides having a higher differential diagnosis accuracy and being easier to improve the necessary diagnostic skill for accurately differentiating diminutive colorectal polyps, NBI has other clinical advantages. First, the conventional endoscopic view can be switched almost instantaneously to the NBI view by pressing a single button on the control handle of the colonoscope, and, second, NBI does not require any dye or staining solution to detect and differentiate neoplastic lesions from non-neoplastic lesions.

In recent years, advancements in the quality of endoscopic images available from high-definition endoscopy and chromoendoscopy have considerably enhanced polyp detection. Although the risk of neoplasia in diminutive polyps is <50%, and the risk of high-grade dysplasia is <2%,[7,32,33] diminutive colorectal neoplasms as well as advanced neoplasms are among the precursors of colorectal cancer, and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[4] It also has been reported that lesions of ≤5

TABLE 2. Effectiveness of training program on diagnostic accuracy

Modality	NEE group: Before-training accuracy (95% CI)	NEE group: After-training accuracy (95% CI)	NEE group: *P* value*	LEE group: Before-training accuracy (95% CI)	LEE group: After-training accuracy (95% CI)	LEE group: *P* value*	HEE group: Accuracy (95% CI)	HEE group: *P* value†
CC	0.43 (0.35-0.50)	0.64 (0.57-0.71)	< .001	0.72 (0.65-0.78)	0.74 (0.67-0.80)	NS	0.74 (0.68-0.80)	NS
NBI-L	0.53 (0.46-0.61)	0.66 (0.59-0.73)	.006	0.65 (0.58-0.72)	0.78 (0.72-0.84)	= .001	0.81 (0.75-0.87)	NS
NBI-H	0.63 (0.56-0.70)	0.74 (0.68-0.80)	< .001	0.73 (0.66-0.79)	0.90 (0.85-0.94)	< .001	0.93 (0.88-0.96)	NS
CE-L	0.68 (0.60-0.74)	0.67 (0.60-0.74)	NS	0.68 (0.60-0.74)	0.76 (0.69-0.82)	NS	0.85 (0.79-0.90)	NS
CE-H	0.63 (0.56-0.70)	0.66 (0.59-0.73)	NS	0.67 (0.60-0.74)	0.81 (0.75-0.87)	= .001	0.85 (0.79-0.89)	NS

NEE, No endoscopy experience; *LEE,* less experienced endoscopist; *HEE,* highly experienced endoscopist; *CI,* confidence interval; *CC,* conventional colonoscopy; *NS,* not significant; *NBI-L,* low-magnification narrow-band imaging; *NBI-H,* high-magnification narrow-band imaging; *CE-L,* low-magnification chromoendoscopy; *CE-H,* high-magnification chromoendoscopy.
**P* values determined by McNemar test comparing before and after training.
†*P* values determined by Fisher exact test comparing LEE after training and HEE.

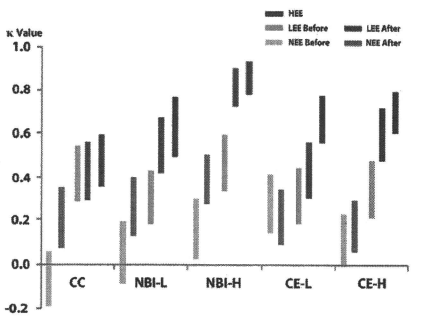

Figure 3. Comparison of 95% confidence interval of κ value for each endoscopic diagnostic modality according to endoscopy experience. Each bar represents the range of 95% confidence interval of the κ value. *HEE,* highly experienced endoscopist group; *LEE,* less experienced endoscopist group; *Before,* before participation in an intensive 1-hour interactive training program; *After,* after participation in an intensive 1-hour interactive training program; *NEE,* no endoscopy experience group; *CC,* conventional colonoscopy; *NBI-L,* low-magnification narrow-band imaging; *NBI-H,* high-magnification narrow-band imaging; *CE-L,* low-magnification chromoendoscopy; *CE-H,* high-magnification chromoendoscopy.

mm make up more than 80% of the colorectal polyps subjected to histopathological assessment.[33] Besides the primary consideration of reducing the risk of future colorectal cancer, the endoscopic differentiation of diminutive neoplastic polyps from non-neoplastic polyps is essential because endoscopists should avoid performing unnecessary procedures, including polypectomies on non-neoplastic polyps, and this also will reduce substantially the number of colorectal polyps requiring histopathological assessment.

There has been considerable interest recently in sessile serrated adenoma (SSA) and serrated adenoma (SA) polyps that also have been associated increasingly with an apparent increased risk of malignant transformation.[34] SSAs endoscopically appear as hyperplastic polyps, but there have not been any published reports as yet applying the Kudo pit pattern analysis to such SSA polyps. In the general population, the prevalence of SSAs has been estimated to range from only 1% to 7% of all polyps, and it further has been shown that most such SSA polyps can exceed 10 mm in size,[35] but we did not detect any SSAs or serrated adenomas in this study. Although it was recently reported that SSAs could be differentiated from hyperplastic polyps by combining NBI and autofluorescence imaging, the report in question had several limitations including the total number of SSAs being relatively small and the lack of any comparison between those two modalities and pit pattern analysis.[36] In addition, the actual prevalence of SSAs is difficult to assess because pathologists have been unable to reach a consensus on the diagnosis of either hyperplastic polyps or SSAs.[37,38] Further studies will be required, therefore, to clarify the endoscopic features and conduct histopathological and molecular-based analyses of SSAs and serrated adenomas.

The primary limitation of our study is that it involved only a small number of polyps. The power of the trial compared to the observed difference was lower because the observed difference was smaller than in the alternative hypothesis used in planning this study. The sample size that was set, however, was not much different from the sample size used in similar studies. Another limitation is that this study was conducted by using endoscopic images. During a "real-time" evaluation, an endoscopist can usually view a detected lesion by using multiple angles and light modalities at variable distances, but we digitally stored all the endoscopic images taken during each exam-

ination, selected the best image from each of the 5 endoscopic observation modalities, and then randomized the distribution order of the images for diagnosis. This process was intended to decrease the likelihood of observational bias and strengthen the reliability of our results, because separate findings based on NBI images and chromoendoscopic images might otherwise have been influenced by the other and made objective evaluation of the individual diagnostic modalities difficult. A third limitation was the relatively short interval between the intensive training program and the follow-up reviews by the NEE and LEE groups. The participants in both groups reviewed all the images for the second time within 24 hours of the training program so as to avoid any possible bias resulting from a feedback learning effect such as self-training. It has previously been reported that feedback received during the development of a diagnostic skill is effective.[39]

In conclusion, NBI, particularly high-magnification NBI, was shown to be a promising tool for diagnostic differentiation of diminutive colorectal neoplastic polyps from non-neoplastic polyps. Expanded training of the LEE group members improved their overall diagnostic ability so that it was equivalent in certain key respects to that of the participating HEE group.

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ORIGINAL ARTICLE

Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: A prospective, randomized, controlled, blinded trial

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Abstract

Objective. To assess whether endoscopic flushes of the bubble-bursting agent Gascon and the mucolytic agent Pronase are as effective in terms of improving endoscopic mucosal visibility as a pre-endoscopic drink of the same agents. ***Material and methods.*** A total of 112 patients attending a Japanese tertiary referral centre for upper gastrointestinal endoscopy were randomized to receive either the standard Japanese procedure of a pre-endoscopic drink of water containing Gascon and Pronase with endoscopic flushes of 20-ml aliquots of water, or no pre-endoscopic therapy but endoscopic flushes of 20-ml aliquots of water containing Gascon, with or without Pronase as necessary. ***Results.*** Visibility scores were significantly better in the pre-endoscopic drink group than in either of the endoscopic flush groups. The group receiving a pre-endoscopic drink required fewer flushes during the procedure and there was no difference in the endoscopic time between the three groups. ***Conclusions.*** Our results suggest that endoscopic spraying of these bubble-bursting and mucolytic agents is not able to offer equivalent improvements in endoscopic mucosal visibility when compared with the standard Japanese therapy of a pre-endoscopic drink of these agents. The addition of Pronase to the spray solution had no measurable benefit over Gascon alone. We therefore cannot recommend endoscopic spraying of mucous clearing agents over their use as a pre-endoscopic drink.

Key Words: *Endoscopy, gascon, mucolytic, pronase, simethicone, visibility*

Introduction

Since the advent of gastrointestinal endoscopy, practitioners have been frustrated by foam and mucous obscuring the field of view. Mucosal toileting techniques with bubble-bursting agents such as Gascon (simethicone) have been used since the 1950s [1–3] and more recent studies have shown that the addition of a mucolytic such as Pronase further improves mucosal visualization [4,5]. These mucosal toileting techniques have become standard practice in Japan [6,7], where cancers tend to be detected earlier than in the West. Patients there are routinely asked to drink 100 ml of water containing 2 ml of Gascon and 20,000 units of Pronase 10 min prior to the endoscopy. These medications are freely available in Europe but it is not usual practice for them to be used. One explanation for this is concern amongst Western endoscopists of an increased risk of aspiration during the procedure if a drink is taken beforehand.

Minimally invasive techniques such as photodynamic therapy and endoscopic mucosal resection (EMR) are now able to offer excellent results for cancers detected at early stages. EMR often offers complete cure but can only be considered for tumours that are well characterized at endoscopy. Detection and characterization of early changes can be achieved through a variety of diagnostic techniques, including chromoendoscopy, high-magnification endoscopy, confocal endoscopy and narrow-band imaging, but all depend upon optimized mucosal views. In addition, chromoendoscopy requires a clear field in order

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that the dye binds to the intended cells rather than the overlying mucous [8,9]. Effective and acceptable mucosal toileting techniques are therefore increasingly vital as advanced endoscopic techniques become used more frequently.

In an attempt to provide the proven benefits of Gascon and Pronase [9–12] without the theoretical increased risk of pulmonary aspiration associated with a pre-endoscopic drink, this study was designed to compare the effectiveness and practicality of spraying Gascon, with or without Pronase, directly onto the mucosa as intermittent flushes through the biopsy channel of the endoscope during the procedure, compared with identical treatment given as a drink prior to endoscopy (conventional Japanese mucosal toileting).

Material and methods

Patients

The Japanese national screening programme for gastric cancer involves the majority of people over the age of 40 years undergoing an annual barium swallow. The tertiary referral centre in which this trial was set accepts patients for gastroscopy either directly (patients with abnormal results on these tests or with appropriate symptoms), or as referrals from other hospitals where early cancers have been detected that are thought to be suitable for EMR. This study was restricted to the screening population because there are differences in the endoscopy technique for those requiring a therapeutic procedure (e.g. the use of zoom scopes and special dyes requiring additional time). A total of 148 of these patients were recruited into this study over a 2-week period. Patients were excluded from the study if they had previously undergone oesophagectomy or gastrectomy, if the endoscopy revealed a lesion requiring a therapeutic procedure such as EMR or if there was active gastrointestinal bleeding or strictures in the upper gastrointestinal tract. The results from 112 patients were therefore available for analysis (Figure 1).

Pre-medication and endoscopic procedure

The study gained ethical approval and informed consent was obtained from all participants. Sealed envelopes were used to randomly allocate patients to one of three groups, as follows. Group S: standard Japanese procedure comprising a pre-endoscopic drink of 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase. During the endoscopy, flushes of 20-ml

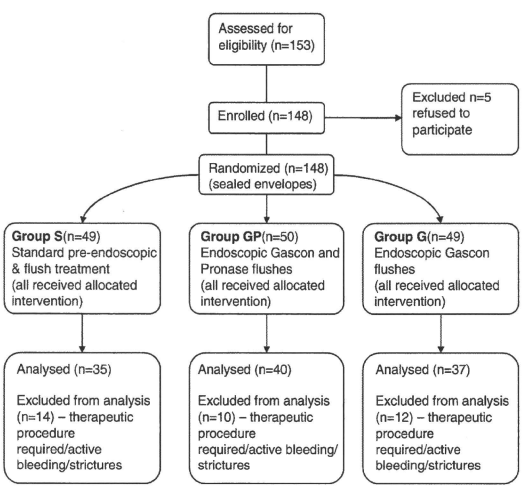

Figure 1. Flowchart showing the disposition of the study patients.

aliquots of water were used as required. Group G: no pre-endoscopic preparation. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water and 2 ml of Gascon were used as required. Group GP: no pre-endoscopic preparation was given. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase were used as required.

All patients underwent routine gastroscopy, including chromoendoscopy, by one of 14 experienced unblinded endoscopists. The endoscopist was free to use as many flushes as deemed necessary to produce a satisfactory view. Once all flushes had been given, one extra photograph was taken from each of four predefined areas: the oesophagogastric junction, the antrum, the lower body and the upper body of the stomach. A record was kept of the total time taken to perform the procedure (from intubation to extubation) and the number of flushes required.

A single, blinded investigator who was experienced in endoscopy but had played no part in the endoscopic procedure then reviewed all of the pictures and assigned each of them a score between one and three for mucosal visibility: 1 = no adherent mucus and clear view of the mucosa; 2 = a thin coating of mucus but not obscuring vision; and 3 = adherent mucus obscuring vision.

The individual scores for each of the four photographs taken were then totalled for each patient to give an overall visibility score ranging from four to 12.

A second blinded investigator separately reviewed and scored the pictures from 20 patients and the results were compared with the original assigned scores.

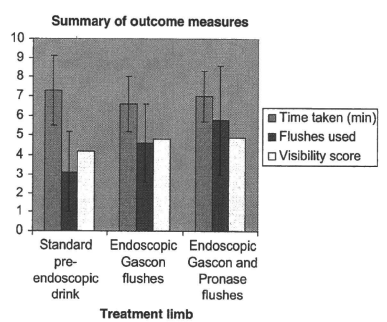

Figure 2. Outcomes.

Statistical analysis

The sample-size calculations showed that 35 participants were required in each treatment group (105 patients overall) to detect a 20% improvement in visibility scores, from 7 to 5.6, assuming a standard deviation of 2 for each group and a power of 90%. Allowing for a 30% attrition rate, we aimed to recruit 150 participants.

Differences between the number of flushes and the time taken were analysed using ANOVA and Fisher's least significant difference. As visibility scores were non-normally distributed, the Kruskal–Wallis and Dwass–Steel–Chritchlow–Fligner tests were used for these results. All analyses used SPSS software (SPSS Inc, Chicago, IL). A *P*-value of 0.05 was taken to be significant throughout.

Results

A total of 112 patients were evaluable in the study, with a mean age of 61 years. The study population comprised 51 males (46%) and 61 females (54%). There were no significant differences between treatment groups (Table I) for a summary of outcome measures please see Figure 2.

Visibility

Visibility scores allocated by the two independent visibility score assessors correlated well (Cohen's weighted kappa 0.604, standard error 0.187, 95% CI 0.237–0.971).

There were significant differences in the visibility scores assigned between groups (H = 17.8, P = 0.0001). The photographs taken from the premedicated Group S scored significantly better for visibility than either of the endoscopic therapy groups GP and G (P = 0.0002 and P = 0.0008, respectively). There was no significant difference in visibility scores between Groups GP and G (P = 0.999).

Table I. Patient characteristics.

	Group		
Characteristic	S (n = 35)	G (n = 37)	GP (n = 40)
Gender; n (%)			
Male	18 (51)	14 (38)	19 (48)
Female	17 (49)	23 (62)	21 (52)
Age (years); mean (SD)	63 (1.9)	61 (1.6)	61 (2.1)

Number of flushes needed

There were significant differences in the mean number of flushes used between groups ($F = 12$, $P = 0.0001$). Significantly fewer flushes were used during the procedure in those patients receiving conventional Japanese pre-medication (Group S) than either of the other groups (Group GP, $P = 0.008$; Group G, $P < 0.001$). In the groups receiving endoscopic flush therapy only, significantly fewer flushes were used in the group with Pronase added to the Gascon mixture ($P = 0.023$).

Time taken for procedure

There was no significant difference in the time taken to complete the procedure between any of the three groups ($F = 2.23$, $P = 0.112$).

Safety

There were no complications in any of the groups. In particular, there were no clinically detectable cases of pulmonary aspiration.

Discussion

Optimal mucosal visualization is vital for thorough endoscopic inspection, particularly when using newer methods such as chromoendoscopy [13–16]. The use of bubble-bursting agents and mucolytics has been shown to improve mucosal visibility in previous trials [17–20], but safety concerns have discouraged generalized use in the West.

We assessed a potentially more acceptable technique of spraying these agents endoscopically. Gascon (simethicone or dimethicone) is silicone-based and non-absorbable, with an excellent safety record. It causes gas bubbles to burst by reducing their surface tension and is marketed for the relief of abdominal bloating. Pronase is a mixture of proteases isolated from *Streptomyces griseus*. These agents were chosen for the study as they both have proven efficacy and have been adopted as standard treatment at the trial centre.

Our results showed that spraying the anti-foam and mucolytic agents endoscopically was not as effective in terms of improved mucosal visibility as pre-endoscopic treatment with the same combination, despite the endoscopist using a greater number of flushes to attempt to clear the mucous. We would ideally have compared the endoscopic flushes with Western standard practice, which in the UK would be to give no pre-endoscopic preparation and to use water endoscopic flushes, but were unable to do this in Japan as using mucous-clearing medication has become so accepted that it was considered unethical not to do so. Adding Pronase to the basic endoscopic flush mixture did not add any advantage in terms of mucosal visibility. The apparent superiority of a pre-endoscopic drink of mucous-clearing solution as compared to endoscopic flush therapy may reflect the more diffuse application of the solution or the 10-min delay between the drink and endoscopy.

No technique resulted in clinically detectable pulmonary aspiration but rates of aspiration during a standard gastroscopy are less than one in a thousand [21] and a larger trial would therefore be needed to properly evaluate this risk.

We conclude that the standard Japanese practice of administering a pre-endoscopic drink containing a mucolytic and anti-bubble agent is superior in terms of endoscopic mucosal visibility to endoscopic application of either both agents or an anti-bubble agent alone. We cannot recommend applying these agents as an endoscopic spray.

Whether improved mucosal visibility results in a higher detection rate of early cancers or improved clinical outcomes remains unknown and well-designed large clinical trials will be needed in the future to evaluate this.

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