Narrow-Band Versus White-Light High Definition Television Endoscopic Imaging for Screening Colonoscopy: A Prospective Randomized Trial

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Background & Aims: **Narrow-band imaging (NBI) has been implemented in gastrointestinal endoscopy to improve the contrast of endoluminal pathologic structures, one of the aims being to increase colonic adenoma detection. Previous studies from referral centers have yielded variable and conflicting results with regard to improvement in adenoma detection rates by using NBI. The present large randomized trial was designed to finally settle this issue.** ***Methods:*** **In a prospective study performed exclusively in a multicenter private practice setting involving 6 examiners with substantial lifetime experience (>10,000 colonoscopies), 1256 patients (men:women, 47%:53%; mean age, 64.4 y) were randomized to HDTV screening colonoscopy with either NBI or white-light imaging on instrument withdrawal. The primary outcome measure was the adenoma detection rate (ie, number of adenomas/total number of patients).** ***Results:*** **There was no difference between the 2 groups in terms of the general adenoma detection rate (0.32 vs 0.34), the total number of adenomas (200 vs 216), or in detection in subgroups of adenomas. This was despite a minimal, but significantly longer, withdrawal time in the NBI group (8.5 vs 7.9 min; $P < .05$). Only hyperplastic polyps were found more frequently in the NBI group ($P = .03$).** ***Conclusions:*** **This large randomized trial in a homogeneous private practice screening setting could not show any objective advantage of the NBI technique over white-light high definition television imaging in terms of improved adenoma detection rate. Contrast enhancement therefore likely will not contribute to a reduction in adenoma miss rates among experienced colonoscopists.**

Screening colonoscopy has been established as an effective means of colorectal cancer prevention in some countries.[1–3] Its effectiveness is based on the earlier detection of cancers and the identification and removal of precursor lesions (adenomas).[3] Colonoscopy, however, still has the drawbacks of poor performance in some cases[4] and of an adenoma miss rate between 10% and 30%.[5] Even if most of the missed adenomas are small and perhaps less important, the efficacy of screening colonoscopy is based on the concept of a clean colon by means of removal of all adenomas found. A higher adenoma detection rate (ADR) is therefore considered a sign of better colonoscopy quality and is used as a quality parameter in most studies.[6]

There have been multiple attempts to improve the diagnostic accuracy of colonoscopy, partly by instrument modification,[7] and partly by image improvement.[8] Total colonic dye staining has been evaluated: there was no overall success, but subgroups of adenomas were found more frequently.[9,10] Flat adenomas in particular may be the most important subgroup with regard to their potential malignancy.[11] Narrow-band imaging (NBI) recently was introduced into gastrointestinal endoscopy, with the expectation that it would replace dye staining for heightening contrast and highlighting lesions. There have been 3 randomized trials from referral centers, with a mixed patient population (screening and diagnostic colonoscopy) that yielded conflicting results.[12–14] In one study including both diagnostic and screening colonoscopy cases, however, the overall adenoma rate was very high, so that further increase appeared to be unlikely.[12] In the second trial, involving diagnostic colonoscopy performed at our center, a 30% increase in ADR was found with NBI, but this difference was not statistically significant; in the same study the significance of the initial difference found with the first 100 cases was gradually lost with increasing patient numbers, leading to speculation that NBI might induce a learning effect for conventional non-NBI colonoscopy also.[13] A recent third randomized study from Asia, however, found a significantly

Abbreviations used in this paper: ADR, adenoma detection rate; HDTV, high-definition television; NBI, narrow-band imaging.

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higher detection rate for adenomas.[14] In addition, a recent single-arm tandem trial found an increased detection rate with the use of NBI for the second withdrawal.[15] With one exception,[13] all other studies used HDTV imaging in both study groups, as we did in the present trial.

We therefore performed a much larger randomized study in a more homogeneous and realistic setting that focused on screening colonoscopy only, and involved only very experienced colonoscopists in a private practice setting.

Patients and Methods

Between March and October 2006 consecutive asymptomatic persons willing to undergo screening colonoscopy (reimbursed in Germany for those >55 y) were asked whether they would be willing to participate in this randomized study. The study was performed in 5 private gastroenterology practices and included 6 experienced examiners. These participating colonoscopists had a lifetime experience of a mean of 19,800 colonoscopies (range, 13,000–28,000) over a mean of 19.4 years (range, 15–28 y). Ethical approval was given by the Charité University Ethical Committee (EA2/018/07).

Wide-angle colonoscopes with high definition television (HDTV) imaging (Olympus Corp, Hamburg, Germany) were used in both study groups. After introduction of the colonoscope into the cecum, patients were allocated randomly to withdrawal of the instrument either using the NBI mode or white-light imaging. Randomization lists were used for allocation to a group in each individual practice. In the NBI group, all switches back to white-light imaging, with the number of occasions and the reasons, were documented. In each participating practice experience with NBI colonoscopy had been available for a few weeks before the start of the study, with 40–50 examinations having been performed. In addition, NBI images of various polyps showing their pit patterns to be different from normal mucosa were made available to the examiners; these images were derived from our previous trial.[13]

Patients' bowel preparation consisted of polyethylene glycol lavage with 4–5 L until clear rectal fluid was evacuated. All examiners took special care to wash and clean the entire large bowel during instrument introduction and withdrawal, to provide optimal imaging conditions. The examination technique was homogeneous among the examiners (ie, at the start the patient was in the left lateral position, and was turned supine in the case of looping and/or need for abdominal compression, with the descending colon/splenic flexure being the usual sites of these eventualities). Spasmolytic agents were not used at instrument insertion and only rarely (if spasm prevented clear views) during withdrawal. No staining technique was applied in any of the study patients. Introduction to the cecum was performed as quickly as possible without special care to look for lesions and no marking of polyps on instrument insertion; inspection and searching for lesions were performed exclusively on instrument withdrawal. In the NBI group, temporary switches to white-light imaging were allowed only when visualization for lesion detection and treatment (polypectomy) subjectively was judged to be inadequate, but these switches had to be limited to short times and small areas before the examiner changed back to NBI.

The following parameters were documented: age and sex of the patient; type and dosage of sedation; examination time, both for instrument introduction and withdrawal; polyp characteristics including size (measured by open forceps or snare), shape (pedunculated/elevated, sessile, and flat, the latter defined as a maximal height of 1.3 mm[16]), and location; histologic findings after polyp removal, using snare polypectomy or forceps removal (for polyps <3 mm), or biopsy if there were contraindications; and other lesions found, such as cancers, diverticula, inflammatory lesions, and so forth.

The *main outcome parameter* was the ADR (number of adenomas/number of patients examined) in the 2 groups. The *secondary outcome measures* included analysis of the total number of all polyps (adenomas/hyperplastic polyps), of flat adenomas (which have been shown repeatedly to have a higher risk of neoplastic development[16,17]), of small adenomas (<1 cm), hyperplastic polyps with size determination, and of right-sided vs left-sided polyp location, in both groups.

Statistical Analysis

The case number calculation for the primary outcome parameter was based on previous ADRs in our hospital-based NBI study, with ADRs of around 20%,[13] and on a previous private practice Berlin colonoscopy project that showed equal polyp detection rates for screening and diagnostic colonoscopy.[18] In the German screening colonoscopy registry, based on self-reporting, adenoma identification rates were in a slightly higher range.[19] We assumed a rate of 20% and based our case number calculation on an increase of this rate by 7% through NBI application, as found in our previous study.[13] It was calculated that a total of 623 cases in each group would be required to detect such a difference with a power of 80% and a significance level of 0.05.

For statistical analysis, continuous variables were compared using the *t* test if normally distributed and the Mann–Whitney test if not normally distributed. Categoric variables were compared using the chi-squared test or the Fisher exact test when appropriate. The chi-squared test and the Fisher exact test were used to analyze the main outcome measure—the difference in the proportions of patients with adenomas.

Table 1. Characteristics of Patients, Indications, and Colonoscopy Performance in Both Groups

Parameter	NBI group (n = 625)	Control group (n = 631)	*P*
Patient data			
Age, mean ± SD (*range*)	64.8 ± 6.5 (50–83)	64.3 ± 7.1 (31–87)	.14
Sex, male	47.0%	47.9%	.78
Sedation[a]			
None	25.8%	25.7%	.97
Midazolam-based regimens	45.6%	44.4%	.35
Midazolam plus propofol	28.6%	29.9%	.33
Mean examination time, min			
Total	14.1 ± 4.4	13.3 ± 3.8	.001
Introduction	5.6 ± 2.5	5.5 ± 2.4	.3
Withdrawal	8.5 ± 3.7	7.9 ± 3.1	.001
Cecal intubation rate	99%	99%	1.0

[a]Midazolam-based regimens included the administration of tramadol in 23.5% (both groups), which was given in addition to the combination of midazolam in 10.7% and propofol in 10.9% of the entire groups.

Results

A total of 1256 outpatients undergoing screening colonoscopy (men:women, 596:660; mean age, 64.4 y; range, 31–87 y) were included, and 625 were randomized into the NBI group and 631 were randomized into the white-light group. Patient characteristics and colonoscopy procedural data in both groups are shown in Table 1. The cecum was reached in 99% of cases; failures were caused by stenosing cancers (n = 4) or a sigmoid stenosis caused by previous diverticulitis. A total of 38 patients were excluded from the study for a variety of reasons. These included identification of 9 carcinomas (4 in the NBI group and 5 in the control group; mentioned in Table 2, but not counted), including the 4 stenosing tumors mentioned earlier. Further exclusions were owing to lost specimens (n = 20); stenosing diverticulitis (see earlier); colons that were dark as a result of melanosis, which were impossible to examine by NBI (n = 2); sigmoid prolapse with failure to introduce the instruments further (n = 1); and other reasons (n = 5).

Results concerning polyps, that is, adenomas and hyperplastic polyps, are shown in Table 2. Overall, 678 polyps, comprising 416 (61%) adenomas and 262 (39%) hyperplastic polyps were found in the study population. Of the adenomas, 15 (3.6%) had the histopathologic diagnosis of high-grade intraepithelial neoplasia.

There were no differences between the 2 groups in the ADR, when analyzed for subgroups in relation to size, form, and location (Table 2, not all details shown). Adjustment for age and sex had no effect on the results either. No differences were found between the first and final 100 patients in terms of ADR. Hyperplastic polyps in general, however, were found more frequently by NBI (Table 2).

In the NBI group, a mean of 0.42 switches to white-light imaging was recorded (range, 0–20); the main reasons for switching were insufficient visualization (28.0% of all switches), and to confirm the presence or absence of lesions with white-light imaging (20.1%). Generally, switches to white-light imaging were more frequent in the initial phase (for the first and last 100 cases the mean values were 1.11 vs 0.17; $P < .001$).

Examples of polyps as seen on white-light and NBI endoscopy are shown in Figures 1 and 2.

Discussion

The present study did not show an improved ADR, either overall or in subgroups, by adding NBI to white-light HDTV colonoscopy. This was a large randomized study on a specific imaging technique in diagnostic endoscopy in general. The case number calculation was set to show even minor differences between the conventional and the new technique at adenoma detection levels already well known from previous studies, both in Ber-

Table 2. Results for Polyp Detection Rates in the NBI and Control Groups

Polyp detection	NBI group (n = 625)	Control group (n = 631)	*P*
All polyps (*n*)	346	332	NS
Patients with polyps (%)	33.4	36.9	NS
Polyps per polyp carrier	1.65	1.42	NS
Polyps <10 mm	317	300	NS
Right-sided polyps	100	107	NS
Left-sided polyps	246	225	NS
Adenomas (*n*)	200	216	NS
Patients with adenomas	22.4%	21.7%	NS
ADR[a]	0.32	0.34	NS
Adenomas per adenoma carrier	1.43	1.58	NS
Adenomas < 10 mm	178	187	NS
Flat adenomas	18	42	.02
Adenomas with HGIN	8	7	NS
Left-sided adenomas	138	146	NS
Right-sided adenomas	62	70	NS
Hyperplastic polyps (*n*)	146	116	.03
Hyperplastic polyps < 10 mm	139	113	.05
Carcinomas (*n*)	4	5	NS

HGIN, high grade intraepithelial neoplasia.
[a]All adenomas/all participants.

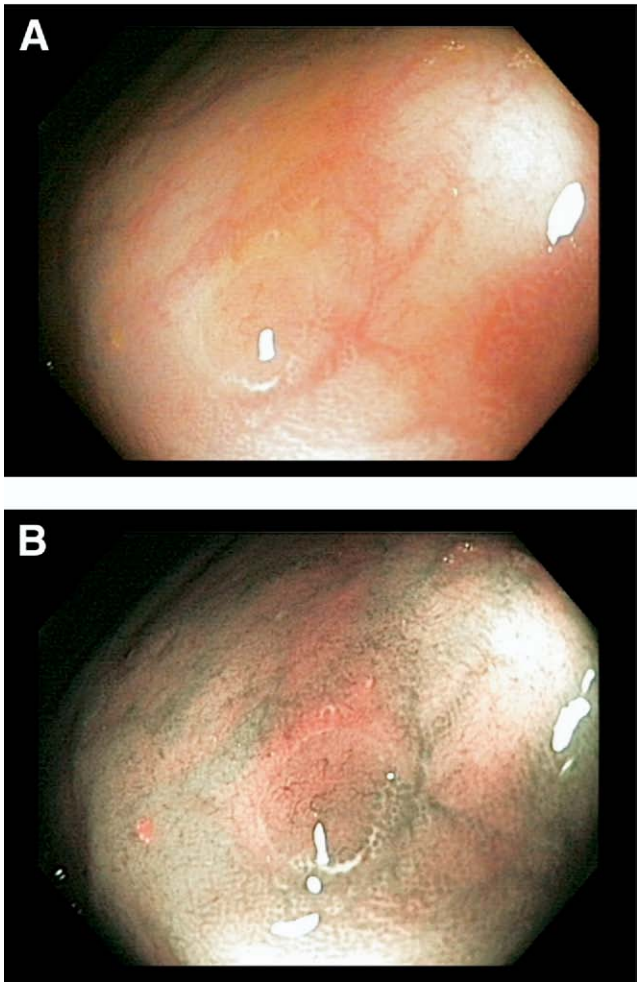

Figure 1. Example of (*A*) white-light vs (*B*) NBI HDTV imaging of a small and flat adenoma.

lin[18] and nationally in Germany.[19,20] Recently, 3 randomized trials were published, with much smaller case numbers (240–400), that examined NBI colonoscopy with regard to ADRs as compared with controls without the use of NBI. However, these studies had conflicting results and left open a number of important questions. The first trial from one well-known US referral center included both diagnostic and screening colonoscopy in a patient group with a very high adenoma rate (around 60%).[12] This adenoma rate was substantially higher than that reported in other recent large-scale US colonoscopy studies with adenoma rates ranging from 14.5% to 37.5%.[21–23] Data from other countries, summarized in Table 3, also showed consistently lower rates.[18,20–27] The second study was performed by us in the setting of a tertiary referral center and included only diagnostic colonoscopy cases. Although there was no overall difference in adenoma detection that reached statistical significance, there were still 30% more adenomas in the NBI group (23% vs 17%), but this difference became gradually smaller with each successive group of 100 cases; thus, we speculated that a learning effect occurring in the control group could be a possible explanation.[13] A recent third study on 243 patients found a significantly higher adenoma rate with NBI (22% vs 14%).[14] In addition, a single-arm study in which tandem colonoscopy was performed with NBI during the second withdrawal found 71% more adenomas by NBI in a total of 40 cases.[15] However, the latter study may not provide the same level of evidence as do randomized trials. Nevertheless, in reviewing the first 2 studies, it could be assumed that with either more cases and/or a population with average adenoma rates, smaller differences between NBI and white-light imaging in the ADR could become obvious.

The present study, despite being multicentric, provided a very homogeneous background with regard to setting (private practice), type of examinations (screening colonoscopies), and examiners (all with experience of >10,000 colonoscopies, reflected in a very high cecal intubation rate of 99%), as well as colonoscopy technique. The ADR of 22% on a patient basis in our trial may be considered relatively low compared with some

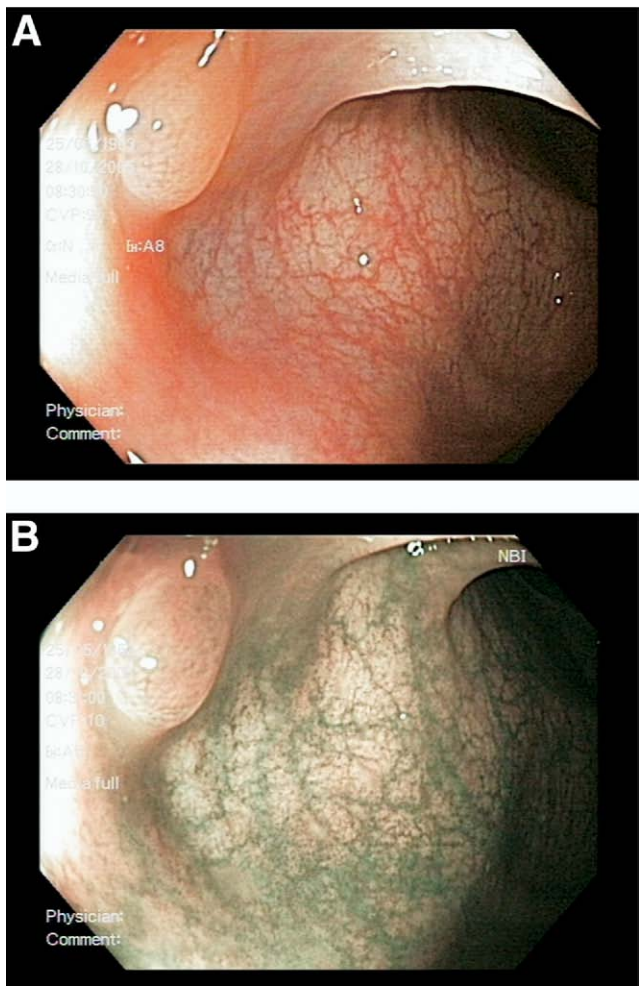

Figure 2. Example of (*A*) white-light vs (*B*) NBI HDTV imaging of a sessile hyperplastic polyp 7 mm in size.

Table 3. ADRs in Large-Scale Screening and Colonoscopy Studies in Various Countries

Study	n	Type of colonoscopy	Adenoma rate (%)
United States			
Kanna et al,[21] 2007	4043	D, S	14.5
Barclay et al,[22] 2007	2053	S	23.5
Lieberman et al,[23] 2000	3121	S	37.5
Germany			
Sieg and Theilmeier,[20] 2006	109,989	D	20
Hüppe et al,[24] 2008	5066	S	10
Adler et al,[18] 2007	1397	D, S	16
Present study	1256	S	22
Poland			
Regula et al[25]	43,042	S	9.4
Israel			
Rainis et la[26]	10,866	D	5
Asia			
Byeon et al[27]	860	S	18.5

NOTE. The percentage of patients with one or more adenomas is shown.
D, diagnostic colonoscopy; S, screening colonoscopy.

rates reported from the United States,[23] partly using HDTV technology.[12] However, this rate is well within the average range to be expected in Western screening studies, even in recent US publications focusing on ADR as the main quality parameter.[22] Variations therefore exist and may depend on a variety of factors. It could be argued that more formal and intensive training with regards to NBI visualization before the start of the study might have improved the ADR. However, we do not know whether such an effect would have specifically increased ADR in the NBI group or also in the control group (leading to similar results but at a higher ADR).

In contrast to all previous NBI studies, this trial was multicentric, and it was performed in private practice settings, almost exclusively the context of screening colonoscopies in Germany. Each participant had extensive prior experience with colonoscopy, and one of the main quality parameters recently highlighted,[22] namely withdrawal times, was within a standard range (mean, 8 min). We consider it very likely that a new method such as NBI will reveal its true value when tested in such a realistic everyday setting; despite the fact that a prospective study per se may improve the results. In fact, in some of the subgroups, the identification rates for sessile and flat adenomas were even higher in the control group, whereas it was expected that these would be the type of polyps that would be more readily and better detected by the contrast-enhancing method of NBI. We can only speculate about the reason for this effect. Insufficient experience with the NBI technique is not a likely explanation because all examiners had sufficient exposure to NBI colonoscopy before the start of the study and the adenoma detection rates were pretty stable throughout the study in both groups. The only effect seen over time was a decreased number of switches from NBI to white-light imaging during the study, which could reflect some effect of familiarization, and also perhaps a waning interest over time in comparing NBI with white-light images. There was even a bias in favor of NBI as shown by slightly, but significantly longer, withdrawal times. The difference in finding flat adenomas in favor of the control group also could be interpreted as a sign of increased difficulty in finding lesions in an image environment considered too dark for routine detection of subtle lesions, but this remains speculative. A recent abstract on a comparative study using tandem methodology found the highest additional yield when NBI was followed by white-light endoscopy, also putting NBI at potential disadvantage; however, no subgroup analysis was performed and the study was not randomized.[28]

The contribution of HDTV vs NBI to these results remains unclear; a recent comparative nonrandomized study could not find any difference in ADR in a small patient number when comparing white-light endoscopy with or without HDTV technology.[29] Three recent abstracts, all based on retrospective analyses, reached contradictory conclusions[30–32] and prospective randomized studies are not yet available. Nevertheless, the very high ADR reported by Rex and Helbig,[12] which could not be increased further by NBI, was attributed by Rex and Helbig[12] to the HDTV effects. Our study used the same technology but did not find such a high rate, being more in line with other reports (Table 3). The adenoma rates in the third randomized NBI study published previously, also using HDTV technology, had higher rates of patients with adenomas (42% vs 34%),[14] but both other studies using HDTV[12,14] included screening and diagnostic colonoscopy cases, which could partly account for these differences.

A further limitation of the study design, as well as of all other previous NBI colonoscopy studies,[12–14] could be that in the NBI group, white-light imaging was used during instrument insertion. This potentially could have contaminated the NBI results, if a substantial number of lesions already had been identified on introduction. In our study, the methodology called for instrument insertion to be performed as quickly and smoothly as possible, without any focus on polyp detection during this phase. The fast mean introduction times (5 min) also would speak against the insertion phase as being of significance for lesion detection in our trial. In any case, it cannot be excluded that adenoma detection would have been different in the NBI group if NBI already had been switched on during introduction, although it appears unlikely that this would have improved results in the NBI group only.

A further probably minor limitation of our methodology is that a temporary switch back to white light was allowed in the NBI group so as not to expose study patients to potential disadvantage if the examiner was

not confident about adequate colonic visualization in individual cases. Except for very rare cases of pseudomelanosis coli, switches happened much more frequently initially and mostly for diagnostic reasons; during the study, the rate dramatically decreased to about 10%, which could be attributed mainly to some kind of internal study learning effect. Polypectomies mostly were performed under NBI mode, but we cannot entirely exclude that some switches for polypectomy may have again influenced adenoma detection results in the NBI group. However, we think that performance of polypectomy under white light usually is focused on the small area within which the polyp is located and the examiners' attention is concentrated on the polypectomy rather than on detection of additional lesions.

The phenomenon that a given test initially shows good or variable results but some accuracy is lost over time, is common in medical imaging studies, and may have to do with limited case numbers, referral center performance, and enthusiasm to report good results. In that respect, testing in a routine setting such as in private practice is a much better reflection of everyday practice than testing that involves highly motivated clinical researchers in a university setting with case selection. The size of the study population may be another factor, with initial good results often being achieved with limited case numbers, which, however, are not confirmed by larger studies.

NBI, nevertheless, still could be useful in 2 respects: first, it could be beneficial for less-experienced endoscopists in helping to improve structure recognition; a potential learning effect even with experienced colonoscopists was suggested in our first study.[13] This aspect, however, has not been studied systematically. Second, similarly to magnification and/or staining colonoscopy,[33–36] in recent reports NBI has been used widely for the differential diagnosis of polyps.[37–39] Such a capability would save biopsy or polypectomy time. In the earlier-mentioned studies, sensitivity was usually in the range of 90%–95%, whereas specificity was between 80% and 90%; a smaller trial showing a poor interobserver agreement regarding NBI pit patterns in diminutive polyps.[40] The sensitivity for chromoendoscopy pit pattern is 64% for European endoscopists versus 68% for Japanese endoscopist, the sensitivity for NBI pit pattern is 77% versus 86% and for vascular pattern intensity 77% versus 91%. The specifity for chromoendoscopy pit pattern is 90% in European endoscopist versus 70% in Japanese endoscopist, the specifity for NBI pit pattern is 60% versus 80% and vascular pattern intensity 50% versus 60%. This, however, means that up to 15%–20% of adenomas are misinterpreted as hyperplastic polyps and perhaps left behind. This may be the reason why none of these methods have been recommended in guidelines as replacements for biopsy or polypectomy of indeterminate colon polyps. However, a reliable method of providing this differential diagnosis would be of great importance in clinical practice, even more so if new imaging methods increase the yield of hyperplastic adenomas. Our current study showed, as did previous studies with NBI[13–15] as well those performed with colonic dye staining,[9,10] a significantly increased rate of detection of hyperplastic polyps. This could be regarded as a negative effect because these polyps would have to undergo a biopsy or be removed to exclude adenomatous tissue with certainty, thus increasing the endoscopists' workload if imaging could not reliably select those lesions that should be removed by forceps or snare.

In summary, we think that our large randomized study has contributed to a definitive answer to the question of whether a method such as NBI may increase the ADR, either overall or in subgroups, in a routine screening setting with highly specialized colonoscopists. Future studies probably should be of similar size and homogeneity to detect minor, but clinically relevant, differences between the new and the conventional methods.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* atwww.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.10.022.

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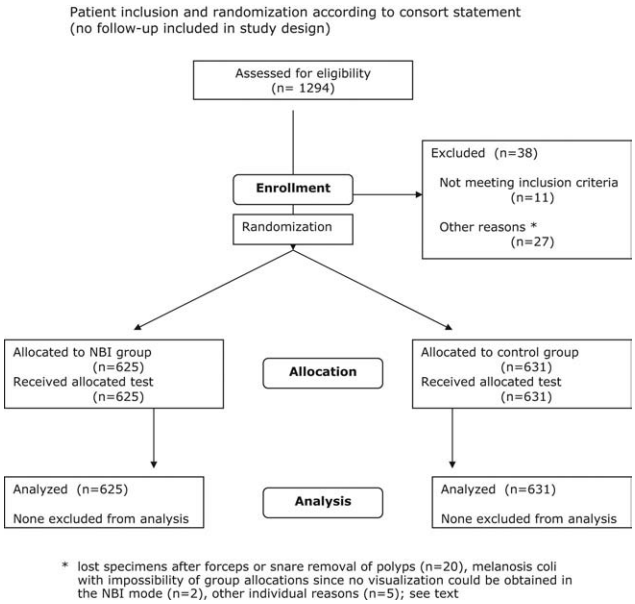
Patient inclusion and randomization according to consort statement
(no follow-up included in study design)
Assessed for eligibility
(n= 1294)
Enrollment
Randomization
Excluded (n=38)
Not meeting inclusion criteria
(n=11)
Other reasons *
(n=27)
Allocated to NBI group
(n=625)
Received allocated test
(n=625)
Allocation
Allocated to control group
(n=631)
Received allocated test
(n=631)
Analyzed (n=625)
None excluded from analysis
Analysis
Analyzed (n=631)
None excluded from analysis
* lost specimens after forceps or snare removal of polyps (n=20), melanosis coli
with impossibility of group allocations since no visualization could be obtained in
the NBI mode (n=2), other individual reasons (n=5); see text

Flow chart.