Advancements in colorectal imaging

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CHAPTER 4

Endoscopic trimodal imaging detects colonic neoplasia as well as standard video endoscopy

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ABSTRACT

Background & aims

Endoscopic Tri-modal Imaging (ETMI) is a novel endoscopic technique combining high-resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI), and has only been subjected to research in expert settings. This randomized controlled trial compared ETMI with standard video endoscopy (SVE) for the detection and differentiation of colorectal lesions in a non-academic setting.

Methods

Patients were randomized for ETMI or SVE and underwent a back-to-back colonoscopy. In the ETMI group, first inspection was done with HRE followed by AFI. In the SVE group, inspection was performed twice with SVE. All detected lesions in the ETMI group were differentiated with AFI and NBI.

Results

A total of 234 patients were included and randomized. In the ETMI group, 87 adenomas were detected during the first inspection with HRE and an additional 34 adenomas were found during second inspection with AFI. In the SVE group, 79 adenomas were detected during the first inspection and 33 additional adenomas during second inspection. Adenoma detection rate between the two groups was not significantly different (ETMI: 1.03 vs. SVE: 0.97, p= 0.360). Adenoma *miss*-rates of HRE and SVE were 29% and 28%, respectively.

Sensitivity, specificity and accuracy of NBI for differentiating adenomas from non-adenomatous lesions were 87%, 63% and 75%, respectively. Corresponding figures for differentiation with AFI were 90%, 37% and 62%.

Conclusion

In a non-academic setting, ETMI did not improve the adenoma detection rate compared with SVE. Both NBI and AFI had high sensitivities and low specificities in the differentiation of colonic lesions.

INTRODUCTION

Colonoscopy is considered the gold standard for the detection of premalignant lesions that are thought to progress into colorectal carcinoma (CRC) following a sequence of events. With the detection and removal of adenomas, a substantial reduction in the expected risk of CRC can be achieved.[1, 2] However, it is estimated that up to 26% of small adenomas are missed during colonoscopy.[3] Furthermore, differentiation of detected lesions can be difficult and many lesions lacking malignant potential are removed without benefit to the patient, as a result of increased time and risks associated with the removal of these lesions.[4, 5]

Several novel endoscopic imaging techniques have been developed which may improve detection and differentiation of gastrointestinal lesions, such as narrow band imaging (NBI) and autofluorescence imaging (AFI). Previous studies have failed to demonstrate an improved detection of neoplasia in the colon by using NBI, whereas its value for differentiation of colonic lesions has proven to be associated with high sensitivity and specificity in experienced hands.[6-11] Concerning the potential of AFI to improve detection and differentiation of colonic lesions, a small number of studies have been performed showing mixed results.[12, 13]

Recently, high-resolution endoscopy (HRE) has been combined with AFI and NBI in a single endoscope with 2 charge-coupled devices, a combination termed endoscopic tri-modal imaging (ETMI). For the purpose of this system, HRE and AFI can be used as a detection technique whereas NBI can serve for differentiation. AFI can furthermore function as an additional detection modality on top of HRE by means of improving the adenoma detection rate.

Nearly all previous studies evaluating NBI and AFI have been performed in expert centres.[6, 8-10, 13] As a consequence, these studies often include a selected patient population and are performed by a small number of endoscopists with extensive experience in advanced clinical imaging. In order to evaluate the true value of these techniques, randomized controlled trials in daily clinical practice in a non-academic setting are needed.

To establish whether ETMI improves the detection of colorectal neoplasia compared with standard video endoscopy (SVE) in regular clinical practice, we conducted a randomized trial of back-to-back colonoscopies comparing ETMI with SVE in six non-academic centres in the Amsterdam region. We also evaluated the additional value of AFI by means of improving the adenoma detection rate. Finally, the diagnostic accuracy for differentiation of colorectal lesions with AFI and NBI was determined.

METHODS

Patients

This study was performed in six non-academic centres in the Amsterdam region and patients scheduled for colonoscopy in one of the centres were screened for participation. Inclusion

criteria were: age > 18 years, surveillance because of a history of adenomatous polyps, a history of colorectal cancer (CRC) for which a partial colectomy was performed, hereditary non-polyposis colorectal cancer (HNPCC) or patients with a positive family history for CRC according to the revised Bethesda criteria.[14] Exclusion criteria were: poor bowel preparation, polyposis syndrome, a history of inflammatory bowel disease, the presence of conditions precluding histological sampling of the colon (e.g. coagulation disorders, anticoagulant therapy) or inability to proceed the colonoscopy due to either mechanical obstruction, a painful colonoscopy or an adverse event. Eligible patients were invited to participate in this study for which written informed consent was needed. Patients were randomly allocated at a 1:1 ratio to ETMI or SVE using block randomization with varying block sizes of 4-8. This study was approved by the medical ethical committees of all participating centres (ISRCTN64206478).

Endoscopic Equipment

In the SVE group, colonoscopy was performed with a standard-resolution, standard (140°) videocolonoscope (Olympus Q140 or Q160, Olympus Europe, Hamburg, Germany). In the ETMI group, colonoscopies were performed with the ETMI system (Evis Lucera, Olympus Inc., Tokyo, Japan). The light source (Lucera, Olympus Inc) contains two rotating red-green-blue filters; one conventional for white light and one additional for NBI, in which the band pass ranges have been narrowed to certain wavelengths (green 530-550 nm and blue 390-445 nm). A high-resolution colonoscope (CF-H240FZL, magnification 100x) was used, containing two charge coupled devices: one for HRE/ NBI and one for AFI. In the AFI mode, blue light (390-470 nm) is used for excitation and green light (540-560nm) for reflection. The endoscopist can easily switch between the three imaging modes by pressing a button on the shaft of the endoscope.

Endoscopic procedure

All patients were prepared by 4L of polyethylene glycol solution (Kleanprep; NorgineGmbH, Marburg, Germany) or 2L of polyethylene glycol solution containing ascorbic acid (Moviprep; NorgineGmbH, Marburg, Germany). Prior to the colonoscopy, subjects were randomized by means of a randomization envelope that was opened. In each patient the whole endoscopic procedure (either HRE-AFI or SVE-SVE) was performed by the same endoscopist who could not be blinded to the imaging intervention. Colonoscopy was performed under conscious sedation with midazolam and/or fentanyl. The colonoscope was advanced to the cecum using HRE or SVE and upon reaching the cecum, the amount of bowel preparation was determined as good (100% mucosa visible), moderate (>90% mucosa visible) or poor (<90% mucosa visible, even after extensive cleaning). Patients with poor bowel preparation were subsequently excluded.

After introduction, each colonic segment (ascending, transverse, descending, rectosigmoid) was inspected twice. In the ETMI arm, first inspection was done with HRE and the

second with AFI. In order to resemble inspection in the ETMI arm, each colonic segment was inspected twice with standard endoscopy in the SVE arm. Special attention was paid not to withdraw the endoscope further during second inspection compared to the first inspection. In case of a very winding colon or an unrecognizable hepatic/splenic flexure, a biopsy was taken at the end of the first inspection as reference.

Endoscopists

All colonoscopies were performed by 8 endoscopists from 6 non-academic centres who had each performed over 2000 colonoscopies. All endoscopists were instructed to perform meticulous inspection and to inspect the colon at least 6 minutes during both examinations. Prior to the start of the study, all endoscopists had performed a minimum of ten colonoscopies with ETMI and received a systematic training including the assessment of colour during AFI and the assessment of the Kudo classification during NBI. The endoscopists previously participated in a study evaluating NBI and AFI during Barrett surveillance as well as in a study assessing differentiation of colonic lesions with NBI and AFI.[15, 16]

Measurements

Intubation and inspection time (excluding cleansing, biopsies and polypectomies) were recorded for each technique with a stopwatch by a dedicated research nurse. All detected lesions were recorded for size, location and macroscopic Paris classification.[17] The size of each lesion was estimated using a biopsy forceps when fully opened. All detected lesions in the ETMI group were differentiated with NBI and AFI. During NBI, magnification was used at the discretion of the colonoscopist and lesions were scored real-time for Kudo pit pattern. Lesions with Kudo pit pattern I-II were considered non-adenomatous and lesions with Kudo pit pattern III or higher were considered adenomatous. During AFI, lesions were scored real-time for colour (green, ambiguous or purple) in which lesions coloured green were considered non-adenomatous and lesions that coloured purple or ambiguous were considered adenomatous. After detection and subsequent assessment with NBI and AFI, all detected polyps were removed. Therefore, detected lesions during the second inspection were missed during the first inspection. Lastly, the accuracy of a previously developed algorithm of NBI and AFI was assessed post-hoc.[15] In this algorithm, all AFI-purple lesions and AFI-ambiguous lesions with Kudo III-V (NBI) were regarded as adenomas. AFI-green lesions and AFI-ambiguous lesions with Kudo I-II (NBI) were regarded as non-adenomatous.

Histopathology

Biopsies were processed and stained using standard methods, and evaluated by a pathologist who was blinded for the endoscopic technique used. Neoplasia was defined according to the Vienna criteria as either low grade or high grade.[18] Lesions diagnosed as sessile serrated adenoma were regarded as non-adenomatous for analysis. An advanced adenoma was

defined as one that was ≥ 1cm, had tubulovillous or villous histological features or high grade intraepithelial neoplasia. The highest grade of neoplasia obtained from any polypectomy specimen during the procedure was used as the final diagnosis in each patient.

Outcome measures

The primary outcome measures of this study were the number of adenomas detected in each arm (SVE vs. ETMI) and the number of patients in each arm with at least one adenoma.

Secondary outcomes were the number of adenomas detected during first inspection with HRE versus SVE, the adenoma miss-rates of HRE (second inspection with AFI) and SVE (second inspection with SVE) and the diagnostic accuracy of NBI and AFI for predicting neoplasia.

Statistics

Normal distributed data were described with the mean and the standard deviation, data with a skewed distribution were described using the median and the inter-quartile range. Means and medians were compared with the independent sample T-test and Wilcoxon Ranksum test, respectively, and proportions were compared with the chi-square test. Logistic regression analysis was performed to estimate the effect size of clinicopathological characteristics of lesions on adenoma miss-rate, expressed in odds ratio and 95% confidence interval (95% CI).

The sensitivity and specificity of NBI and AFI for differentiating adenomatous from non-adenomatous lesions was assessed by comparison with histopathology which was used as the reference standard diagnosis. The accuracy of NBI, AFI and the algorithm of NBI and AFI were compared with McNemar's test for paired data. The part of the manuscript on diagnostic accuracy of NBI and AFI was reported according to the STARD statements for diagnostic accuracy studies.[19]

Sample size

The sample size calculation was based on a previous study that demonstrated a mean number of detected adenomas of 0.36 per patient per colonoscopy.[20] A 30% increase in detection rate with ETMI was set as clinically relevant. Power was set at 80% with a significance level of 5%. The calculated sample size was therefore 234 patients.

RESULTS

Patient characteristics

Between July 2007 and February 2010, 258 patients gave informed consent and underwent colonoscopy of which 24 were excluded; 15 patients were excluded because of poor bowel preparation, 6 because of technically difficult and painful colonoscopy, 2 because of a mechanical obstruction and 1 due to bradycardia (figure 1).

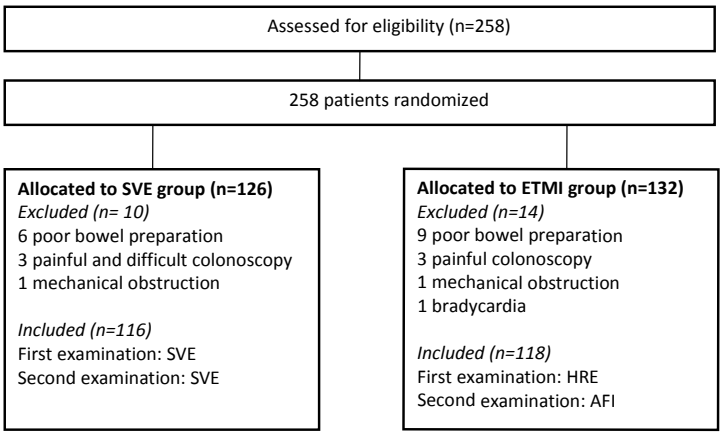

Figure 1: flow diagram of patient inclusion

Out of the 234 included patients, 118 underwent colonoscopy in the ETMI group and 116 in the SVE group. The average insertion time was 10.02 min (range 1.19 – 35.15 min) in the ETMI group and 8.23 min (range 2.30 – 23.45 min) in the SVE group (p=0.021). Insertion time was not significantly different between endoscopists (p=0.621). No adverse events occurred. Characteristics of included patients are described in table 1. Except for the inspection time being significantly longer in the ETMI group during both first (7.06 min. vs. 6.18 min., p=0.025) and second inspection (7.34 min. vs. 6.06 min., p<0.001), there were no significant differences in patient characteristics between the two groups.

Four of the 8 participating endoscopists performed over 25 colonoscopies, the other four performed less than 25 (range 12- 78).

Table 1 Characteristics of included patients

Characteristics included patients			
	SVE (n= **116**)	ETMI (n= **118**)	p value
Male n (%)	67 (58%)	61 (52%)	**0.352**
Mean age yrs (SD)	59 (14)	59 (14)	**0.960**
Indication			
Polyp surveillance	59	49	**0.259**
CRC surveillance	10	14	
HNPCC	7	10	
Family history CRC	40	45	
Colon preparation			
Good	71	81	**0.233**
Moderate	45	37	
Median interval to previous endoscopy, yrs (IQR)	2.3 (0.6 – 3.7)	2.6 (0.9 – 4.8)	**0.459**
Inspection time -min (SD)			
First session	6.18 min (2.44)	7.06 min (2.41)	**0.025**
Second session	6.06 min (2.33)	7.34 min (2.41)	**<0.001**
Patients with previous colectomy	11	13	**0.715**

Adenoma detection per group

In the ETMI group, 87 adenomas were detected in 42 patients during first inspection with HRE, of which 46 were advanced adenomas (table 2). During the second inspection with AFI, another 34 adenomas were detected in 25 patients, of which 12 were advanced. Nine patients had adenomas detected during the second examination with AFI only. The adenoma miss-rate of HRE when a second inspection was done with AFI was 28.1% (95% CI: 20.8-36.7) and the advanced adenoma miss-rate was 20.7% (95% CI: 12.3-32.8).

Table 2 Comparison of polyp- and adenoma detection rate per group

Number of detected lesions per examination per group and number of patients with detected lesions per examination per group				
		ETMI *(I:HRE, II:AFI)*	**SVE** *(I:SVE, II:SVE)*	**p value**
No of polyps	**I***	184	199	**0.786**
	II (%)**	72 (28.1%)	100 (33.4%)	
Patients with polyp(s)	**I** (%)	68	73	**0.407**
	II (%)	41 (37.6%)	55 (43.0%)	
No of adenomas	**I**	87	79	**0.360**
	II (%)	34 (28.1%)	33 (29.5%)	
Patients with adenoma(s)	**I** (%)	42	45	**0.613**
	II (%)	25 (37.3%)	23 (33.8%)	
No of advanced adenomas	**I**	46	33	**0.447**
	II	12 (20.7%)	14 (29.8%)	
Patients with advanced	**I**	26	21	**0.453**
Adenoma(s)	**II** (%)	10 (27.8%)	14 (40.0%)	
No of carcinomas	**I**	3	7	**0.188**
	II (%)	0 (0%)	0 (0%)	
Patients with carcinoma	**I**	3	7	**0.187**
	II (%)	0 (0%)	0 (0%)	

In the SVE group, 79 adenomas were detected in 45 patients during the first inspection, of which 33 were advanced adenomas (table 2). During the second inspection another 33 adenomas were detected in 23 patients, of which 14 were advanced adenomas. Nine patients had adenomas in the second examination with SVE only. The adenoma miss-rate of SVE was 29.5% (95% CI: 21.8-38.5) and the advanced adenoma miss-rate was 29.8% (95% CI: 18.7-44.0).

The mean number of adenomas detected during both examinations with ETMI was 1.03 (SD 1.75) and 0.97 (SD 1.52) with SVE, which was not significantly different (p=0.360). During the first examination only, the mean number of adenomas detected with HRE was 0.68 (SD 1.20) and 0.74 (SD 1.43) with SVE, which was not significantly different either (p=0.360). Size, shape and location of missed adenomas were not significantly different between the two groups; p=0.695, p= 0.125 and p=0.876, respectively. Missed polyps and adenomas are described per size group in table 3.

Table 3

	Lesion miss-rate, % (95% CI)					
	0-4 mm		ETMI (I:HRE, II:AFI)5-9 mm		≥ 10 mm	
	SVE	ETMI	SVE	ETMI	SVE	ETMI
Non-adenoma	37.3% (29.4-46.0)	34.9% (25.6-45.7)	33.3% (21.0-48.4)	18.2% (8.6-34.4)	31.2% (15.4-54.0)	15.8% (5.5-37.6)
Adenoma	29.5% (19.6-41.9)	39.3% (27.6-52.4)	32.4% (19.1-49.2)	23.7% (13.0-39.2)	23.5% (9.6-47.3)	11.1% (3.9-28.1)
Advanced adenoma*	50.0% (28.0-72.0)	43.8% (23.1-66.8)	16.7% (4.7-49.1)	23.1% (8.2-50.3)	23.5% (9.6-47.3)	11.1% (3.9-28.1)

* = Advanced adenoma defined as adenoma ≥ 1 cm, with villous histologic features or with high-grade dysplasia

Overall polyp and adenoma characteristics

Overall, 555 lesions were detected in 161 patients during both inspections, of which 25 were lost for histology and excluded for analysis. A total of 233 adenomas were detected, of which 105 were advanced. Size was significantly associated with adenoma miss-rate, with larger adenomas (≥ 10mm) being missed less often than small adenomas (< 10 mm) (OR 0.41; 95% CI: 0.17 – 0.97). Shape (flat vs. protruded) and location (proximal vs. distal) was not significantly associated with adenoma miss-rate; OR 0.92 (95% CI: 0.48 -1.76) and OR 0.86 (95% CI: 0.48 – 1.53), respectively.

Small advanced adenomas (< 10 mm) were significantly more often missed than large advanced adenomas (OR 0.32; 95% CI: 0.12 – 0.90). Shape or location was not significantly associated with advanced adenoma miss-rate; OR 0.87 (95% CI: 0.30 – 2.54) and OR 0.75 (95% CI: 0.31 – 1.85), respectively.

Out of the 26 missed advanced adenomas, 6 were large (≥ 10 mm) and the remaining 20 were advanced as a result of histopathology (16 tubulovillous adenomas with LGD, 3 villous adenomas with LGD and 1 villous adenoma with HGD).

Diagnostic accuracy of NBI and AFI for differentiation

A total of 256 lesions were detected in the ETMI group and subsequently classified with AFI for colour and with NBI for Kudo pit pattern. The endoscopist was unable to classify with NBI in 18 lesions and with AFI in 17 lesions. Sensitivity, specificity and accuracy of NBI were 87% (95% CI: 80-92), 63% (95% CI: 54-71) and 75% (95% CI: 69-80), respectively (table 4a). Corresponding figures for AFI were 90% (95% CI: 83-94), 37% (95% CI: 29-45) and 62% (95% CI: 56-68) (table 4b). Sensitivity of AFI and NBI were not significantly different (p=0.797). Specificity (p<0.001) and accuracy (p=0.001) were significantly higher with NBI compared with AFI.

Furthermore, the accuracy of a previously developed algorithm of NBI and AFI was assessed.[15] In the current study sensitivity, specificity and accuracy of this algorithm were 88% (95% CI: 81-93), 58% (95% CI: 49-67) and 73% (95% CI: 67-78), respectively (table 4c). The algorithm contained 14 false negatives, of which 13 were green on AFI and 51 false positives of which 41 were purple on AFI. The accuracy of the algorithm was significantly higher than

Table 4a Correlation of NBI and histopathology

	Histopathology		
NBI	neoplastic	non-neoplastic	
Kudo ≥ III	101	45	*ppv* 69.2%
Kudo I, II	15	77	*npv* 83.7%
	sensitivity 87.1%	*specificity 63.1%*	238

ppv: positive predictive value, *npv*: negative predictive value

Table 4b Correlation of AFI and histopathology

	Histopathology		
AFI	neoplastic	non-neoplastic	
(light) purple	104	78	*ppv* 57.1%
green	12	45	*npv* 78.9%
	sensitivity 89.7%	*specificity 36.6%*	239

Table 4c Correlation of algorithm of NBI + AFI and Histopathology

	Histopathology		
NBI + AFI	neoplastic	non-neoplastic	
suspicious	101	51	*ppv* 66.4%
not suspicious	14	71	*npv* 83.5%
	sensitivity 87.8%	*specificity 58.2%*	237

the accuracy of AFI alone (p=0.001) but not significantly better than the accuracy of NBI alone (p= 0.571).

DISCUSSION

The current study reports on the potential of ETMI in the detection of adenomas compared to SVE in a non-academic setting. Many endoscopic studies on advanced imaging of the colon are performed in tertiary centres, and there is a need to ascertain if these new imaging techniques improve detection and differentiation of colonic lesions in the community and non-specialised settings.[8, 10, 12, 13, 21-26] Our results demonstrate that ETMI did not improve adenoma detection rate compared with SVE, despite a significantly longer inspection time which is known to positively influence adenoma detection rate.[27] Moreover, AFI proved to have no additional value compared to SVE by means of increasing adenoma detection.

During the first examination, no difference in adenoma detection rate was found between SVE and HRE which is in concordance with several prospective studies including one ran-

domized trial that have also failed to show a higher adenoma detection rate using HRE.[28-31] In contrast, a recent retrospective study from the Mayo Clinic Jacksonville found a higher adenoma detection rate with high-definition colonoscopy compared to standard white light endoscopy.[32] Although this study appears well controlled in many regards, it is limited by its retrospective nature in which data such as inspection time could not be collected.

During the second examination, no additional improvement in adenoma detection rate with AFI was obtained compared with SVE. Previously, a number of studies assessing the value of AFI as a primary detection modality have shown conflicting results.[12,13] A recent study by Ramsoekh *et al* using autofluorescence endoscopy (AFE), a modality similar to AFI although utilizing fibre optic endoscopy instead of video endoscopy, demonstrated a significant improvement in the detection of adenomas in a high-risk group of patients.[33] Even though this study was well executed, the mean withdrawal time was significantly longer during AFE, which could be a potential source of bias. Further studies assessing the potential of autofluorescence as a primary detection modality are warranted, although the results of our study suggests that AFI does not have an additional value in a non-academic setting.

The adenoma miss-rate in our study was substantial without any significant difference between the two arms, despite the fact that patients with poor bowel preparation were excluded and inspection time was more than 6 minutes in most colonoscopies. The majority of the missed large adenomas (≥ 10 mm) was flat (71%) and situated in the proximal colon (86%), factors that are known to be associated with a higher miss-rate.[5, 34, 35] Miss-rate for large adenomas per arm ranged from 11% (3/27) in the ETMI arm up to 19% (4/21) in the SVE arm, which is above the reported 95%-confidence interval of 1-8% missed large adenomas described in a systematic review.[3] Since all studies included in this systematic review were conducted in an academic setting, our high miss-rate of large adenomas might reflect true clinical practice.

Effective CRC prevention has also been closely related to the detection and removal of advanced adenomas. Patients with advanced neoplasia are more likely to develop interval advanced lesions and cancer compared with patients who did not have advanced lesions at baseline colonoscopy.[1, 36] Miss-rates for advanced adenomas in our study ranged from 20.7% in the ETMI arm to 29.8% in the SVE arm. Again, this is higher than previously reported miss-rates of advanced adenomas, ranging from 5.7% to 11% in recently conducted trials.[5, 10] Our findings of a rather high miss-rate for advanced adenomas could be a result of the fact that 55% of all advanced adenomas were small tubulovillous adenomas. Because histopathology was not subjected to central review, overreading of advanced histology could have occurred.[37] Even so, when this group of small tubulovillous adenomas was not considered to be advanced, overall *miss*-rate for advanced adenomas would decrease to 14.6% which is still somewhat higher than a recently conducted trial including 294 patients in 11 centres.[5] Possibly, endoscopists in an academic setting, who are often more extensively trained and specialized in performing colonoscopies, miss less lesions.

Concerning the *differentiation* between adenomatous and non-adenomatous lesions, both NBI and AFI had a high sensitivity but a low specificity in our study. Ideally, the sensitivity of modalities that aid in differentiation of colonic lesions approaches to 100%, in order not to leave any adenomas in situ. Consequently, a high sensitivity is considered more important than a high specificity in differentiating lesions. In the current study, NBI and AFI had a sensitivity of 87% and 90%, respectively, which is deemed clinically unacceptable, as approximately 10% of all detected adenomas would be left in situ.

The accuracy of NBI alone obtained in this study appears relatively low when compared to literature, demonstrating a higher accuracy with NBI, including a systematic review showing an accuracy of 89% (95% CI: 87-91%).[6-8, 24, 38, 39] However, the majority of these studies differentiated lesions post-hoc and not real-time as we did, which could explain for our lower accuracy. The few studies that differentiated real-time with NBI also found a higher accuracy of NBI compared to our results, but these studies included a small number of expert endoscopists.[8, 40] Interestingly, a previous study that included the same endoscopists as in the current study showed a similar accuracy with NBI of 70%.[15] Therefore, the level of experience of the endoscopists could also have contributed to the accuracy in our study.

An algorithm of NBI and AFI that previously led to maintaining the high sensitivity of AFI (96%) together with an acceptable specificity of 69% proved to be unsatisfactory in the current study due to a number of reasons. Firstly, sensitivity of the algorithm was lower than that of AFI alone because a number of lesions considered ambiguous during AFI were differentiated incorrectly as non-adenomatous during NBI. Secondly, the majority (76%) of lesions incorrectly differentiated as adenomas during AFI were considered purple and therefore not differentiated with NBI. As a consequence, specificity of the algorithm showed to be only 58%. Although this was significantly better than the specificity of AFI alone, it is still lower than the specificity found in our previous study. Again, this may be a result of our real-time differentiation.

A potential shortcoming of the current study is the minimal number of 10 endoscopies that were performed by the participating endoscopists prior to the start of the study, which could be considered too little. Although there have been no previous studies on the learning curve for detection with AFI, we believe 10 endoscopies were sufficient for our endoscopists to optimize their detection skills with AFI, especially since all endoscopists received a teaching session for the differentiation of lesions with AFI and NBI and had personal experience with ETMI in upper gastrointestinal endoscopy. Recent studies have shown that a teaching session improves the diagnostic ability and that a high accuracy can be achieved.[41, 42] Another potential shortcoming could be that 17.5% of included patients were high-average risk (CRC surveillance, HNPCC) who could have disproportionally contributed to adenoma detection and miss-rate of (advanced) adenomas. When we excluded this group of patients, however, detection and miss-rate of both adenomas and advanced adenomas did not alter (results not shown). Lastly, the design of our study does not enable us to address the potential of NBI to improve adenoma detection, since NBI was used as a differentiation modality only.

Nearly all studies evaluating new imaging modalities in colonoscopy have been performed in expert centres. Before these modalities become widely available, their value needs to be assessed in non-expert settings also. Because this study was conducted real-time and amongst non-academic endoscopists, we believe our results reflect regular clinical practice. In conclusion, ETMI did not improve the adenoma detection rate compared to SVE in a non-academic setting. We also demonstrated that a substantial number of adenomas were being missed by both SVE and HRE and the additional value of AFI on top of HRE to improve adenoma detection was unsatisfactory. Regarding the differentiation of colonic lesions, both AFI and NBI had a high sensitivity but a low specificity. Although an acceptable threshold for accuracy of differentiation of colonic lesions is not fixed, the accuracy of AFI and NBI in this study was deemed insufficient for clinical use.

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