Thieme

Effects of two instrument-generation changes on adenoma detection rate during screening colonoscopy: results from a prospective randomized comparative study

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ABSTRACT

Background Previous studies have shown that multiple colonoscope features have to be changed before an improvement in adenoma detection rate (ADR) becomes obvious, such as with changing from one instrument generation to the next but one. We wanted to evaluate whether such an effect can also be observed in a private-practice screening setting.

Methods In a randomized study, we compared the latest generation colonoscopes from one company (Olympus Exera III, 190) with the next to last one (Olympus 165), including only patients presenting for screening colonoscopy. The primary outcome was ADR achieved with 190 colonoscopes (190-C) in comparison with 165 colonoscopes (165-C).

Results 1221 patients (46.1 % men; mean age 62.2 years, standard deviation 6.6) were included (599 screened with the Olympus Exera III, 190). The ADR difference in favor of the 190-C instrument (32 % [95 % confidence interval (CI) 26 % to 39 %] vs. 28 % [95 %CI 22 % to 34 %] in the 165-C group) failed to reach statistical significance ($P = 0.10$); only the rate of small (< 5 mm) adenomas was significantly increased at 22.5 % (95 %CI 19 % to 26 %) vs. 15.6 % (95 %CI 13 % to 18 %; $P = 0.002$). Furthermore, significantly more adenomas were found in the 190-C group, with an adenoma rate (all adenomas/all patients) of 0.57 (95 %CI 0.53 to 0.61) vs. 0.47 (95 %CI 0.43 to 0.51; $P < 0.001$).

Conclusions This randomized comparative trial in a private-practice screening setting only partially confirmed the results of prior studies that, with multiple imaging improvements achieved over two instrument generations, an increase in overall adenoma number becomes measurable.

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Introduction

Colonoscopy quality is crucial to achieve the desired outcomes of the examination, namely to reduce the occurrence of colorectal cancer by finding early stage cancers as well as colorectal adenomas as precursor lesions [1]. These goals are especially relevant in the screening setting [2]. The main quality parameter to measure outcome is therefore believed to be the so-called adenoma detection rate (ADR) [3]. This assumption is based on studies that have correlated interval cancer rates with the ADRs of the colonoscopists [4, 5].

Measures to increase ADR have therefore been the focus of numerous studies dealing with improved endoscope imaging features. However, improvements of only one of these instrument features, such as widening of the angle of view, using high definition television (HDTV) imaging, or image postprocessing (e. g. narrow-band imaging [NBI], Fujinon intelligent chromoendoscopy [FICE], or I-Scan), have not led to a consis-

tent ADR increase. Several meta-analyses have summarized this lack of effect on ADR of HDTV [6] and image enhancement techniques [7] (the most recent); however, conflicting results were recently reported on widening of the endoscopic angle of view [8–10].

Therefore, it could be speculated that it may take several imaging changes, such as those associated with technical progress developed over two colonoscope generations – i. e. comparing the latest instrument generation with the next to last one – before improvements in ADR can be measured. This hypothesis was based on two previous retrospective studies from our group [11, 12] and was recently confirmed for diagnostic colonoscopy in a prospective randomized diagnostic tandem study in a hospital setting [13]. We have now tested this hypothesis in a different setting, namely a private-practice screening colonoscopy setting, with a group with whom we have previously performed several larger randomized colonoscopy trials [14–16].

Methods

Study design

The study was a prospective multicenter 1:1 randomized study involving seven private-practice gastroenterology offices with a total of 14 experienced examiners (> 2000 colonoscopies), which was performed between November 2013 and September 2016 (sets of instruments were made available to 3–4 centers each during 6–12 months). The study was approved by the ethical committee of the Hamburg Chamber of Physicians (PV4343). All authors had access to the study data and reviewed and approved the final manuscript.

Study population

Patients were selected from the screening colonoscopy list (age ≥ 55 years), with further inclusion criteria being a status of 1 or 2 on the American Society of Anesthesiologists (ASA) classification and having provided signed informed consent.

Exclusion criteria were the following:

- symptoms indicative of colorectal disease, such as colonic bleeding, significant diarrhea, obstipation, and change in bowel habit
- known colonic disease for further evaluation (e. g. inflammatory bowel disease [IBD], polyps for resection)
- surveillance after polypectomy or colon tumor surgery
- use of anticoagulants that would prevent biopsy or polypectomy
- poor general condition (ASA III or more)
- incomplete colonoscopy planned.

Study procedure

Randomization and study groups

After they had given informed consent, patients were randomized in each center using sealed envelopes per center to one of the two study groups:

a) 190-C group (intervention group), examination with the latest generation colonoscope (190 series CF or PCF colonoscopes; Olympus Corp., Hamburg, Germany)
b) 165-C group (control group), examination with the 160/5 generation colonoscope (Olympus Corp.).

Instrument specifications and changes over generations

The main differences between the 190 colonoscopes and those from last but one generation (165) were: standard definition TV (SDTV; 576 lines) vs. HDTV (1080 lines; the latter being introduced in the intermediate 180 generation); a differentiated depth of field, improved near- and far-focus resolution (both constantly improved from the 165 to the 180 and to the 190 generation); wider angle of view (160° near and 170° far vs. 140° for the 165 and 180), brighter NBI features (improved versus the 180 scope), and processor improvements [13].

Colonoscopy performance and histologic analysis

Each patient underwent bowel preparation in accordance with the local practice of the office. Bowel cleansing quality was assessed using a modified combined "Boston Bowel Preparation Scale" as in previous studies [14, 15], as well as according to the recent German endoscopy quality guidelines [17]. Briefly, the entire colon was assessed and scored (instead of segmental scoring) as follows: 0 = largely unprepped colon, large areas not visible due to residual stool and/or dark fluid; 1 = only parts of the colonic mucosa visible because of stool and dark fluid; 2 = small amounts of residual stool, small stool fragments and/or dark fluid, but colonic mucosa adequately visible in the majority of the colon; 3 = entire colonic mucosa clearly visible, no residual stool (fragments) or dark fluid.

Sedation quality was assessed on a subjective score of 1–6, ranging from complete sedation with no pain reaction (1) to colonoscopy being stopped because of patient intolerance (6). Introduction and withdrawal times were measured, and times required for biopsies and polypectomies were considered separately i. e. overall and diagnostic-only withdrawal times were recorded separately. NBI was used at the discretion of the endoscopists once polyps or unclear findings were seen, but none of the study colonoscopies in the 190 group was done with NBI as a routine.

Polyps were documented with regards to location (cecum, ascending, transverse, and descending colon, sigmoid and rectum), size (open forceps or snare for comparison), and morphology using the Paris classification (polypoid pedunculated or sessile, non-polypoid slightly elevated/flat/depressed) [18]. Polyps were then resected using biopsy forceps or cold snare (for polyps < 5 mm) or conventional polypectomy according to local standards.

The histology of the resected polyps was analyzed by local private practice specialist gastrointestinal pathologists using the Vienna classification [19, 20] with regards to dysplasia grade and the presence of serrated adenomas; final histologic categories were hyperplastic or adenomatous (tubular, villous, tubulovillous, sessile serrated adenoma/polyp [SSA/P]). Because of the very high likelihood of them being hyperplastic,

small whitish distal rectal polyps were not systematically biopsied or resected.

Outcomes

The main outcome variable was the ADR using 190 colonoscopes in comparison with the 160/5 colonoscopes at the patient level. The ADR was defined as the percentage of patients with at least one adenoma. In the calculation of the ADR, tubular, villous, tubulovillous, and SSA/Ps were included, but invasive carcinomas (with or without adenomatous components) were not.

The secondary outcomes for this study for both groups were:

- the number of adenomas in relation to the case numbers, i. e. (overall) adenoma rate (all adenomas/all patients) in both groups
- the mean number of adenomas per adenoma carrier (mean number of adenomas in all patients with at least one adenoma) in both groups
- differences in adenoma subgroups by size (≤1 cm, >1 cm), form (flat, sessile, pedunculated), and location (right sided = to left hepatic flexure, left sided = descending colon, sigmoid, and rectum), and histologic subgroups (including dysplasia grade, low/high grade intraepithelial neoplasia, and SSA/P)
- the cecal intubation rate
- complications in both groups.

Sample size calculation and statistics

Previous large-scale studies by our group have shown ADRs with different generation instruments of between 18 % and 22 % [11], so 20 % was taken as the basis for the case number calculation for the control group. To increase the ADR by a third (i. e. from 20 % to 27 %) by skipping one instrument generation was assumed to be sufficiently clinically relevant. Given these assumptions, 575 colonoscopies per group were required to reveal this difference (power 80 %, two-sided $\alpha = 0.05$).

The ADRs of both groups were estimated using a multilevel logistic regression with respect to the cluster structure: patients were nested within examiners and examiners were nested within private-practice gastroenterology offices. The expected number of adenomas per adenoma carrier was estimated using a multilevel Poisson regression with respect to the cluster structure. For both models, adjusted estimators and the corresponding 95 % confidence intervals (95 %CI) for both groups and the resulting group differences with 95 %CI were reported. For all subgroup analysis, raw proportions with corresponding 95 %CI and unadjusted group comparisons were reported.

To quantify the extent explained by the endoscopist/practice with regard to variation in the individual probability for adenoma detection adjusted for colonoscopes, the endoscopist/practice-specific median odds ratio (MOR) was determined [21]. An MOR equal to 1 indicates no variance at the endoscopist/practice level.

Results

Between November 2013 and September 2016, a total of 1221 patients were enrolled in seven centers, including 14 examiners; the number of cases included by each examiner ranged from 30 to 121. Patient and colonoscopy characteristics are shown in ▶ **Table 1**; there were no differences between the groups in any of the variables.

Among the 926 detected polyps, histopathological evaluation was missing for 12 polyps found in 11 patients (6 patients in the 190-C group and 5 patients in the 165-C group) because the polyps were lost after resection. Some cases had incomplete documentation (usually <10) for some of the variables, such as lesion form and size, and were not included in the calculation of the denominator. No major complications were documented; two intraprocedural bleeds were managed endoscopically.

Results with regards to adenoma rates including subgroups are shown in ▶ **Table 2**. Overall the ADR in the entire study population was 32.7 %. The ADR was increased by 4 percentage points (95 %CI 1 to 9 percentage points), with the 190-C at 32 % (95 %CI 26 % to 39 %) compared with 28 % (95 %CI 22 % to 34 %) for the 165-C, but this failed to reach statistical significance ($P = 0.10$). On the basis of this interim analysis, a total of 4120 patients would have been required to show a significant ADR difference of 4 percentage points (power 80 %, $\alpha = 0.05$), so the study was terminated.

In terms of the secondary outcomes however, more adenomas were found in the 190-C group (calculated as the rate of all adenomas/all patients) with 0.57 vs. 0.47 ($P < 0.001$). There were also significant differences in some of the subgroups of adenomas, especially smaller adenomas, in favor of the 190-C instrument, e. g. with regards to small adenomas and adenoma distribution (see ▶ **Table 2**). We also analyzed the influence of possible differences between examiners with regards to probable ADR differences and found that the $MOR_{practice}$ was 1.25 (95 %CI 1.06 to 2.24), while the $MOR_{endoscopist\ within\ practice}$ was 1.32 (95 %CI 1.13 to 1.86), which is in the same range as the ADR differences caused by the two endoscope-generation changes.

Example images of polyps visualized with the two endoscope generations are given in ▶ **Fig. 1**.

Discussion

The main purpose of colonoscopy, either diagnostic or screening, is to detect cancers at an early stage and, even more so, to find and remove adenomas as precursor lesions, in order to prevent the occurrence of colorectal cancer. The ultimate variable for colonoscopy outcome quality is therefore the rate of missed or interval cancers. Because this requires meticulous follow-up and large colonoscopy numbers per colonoscopist, surrogate variables have been defined, such as the ADR, and correlation of the ADR with the rate of interval cancers has been shown in two large studies [4, 5]. Therefore, the ADR has become the holy grail of colonoscopy quality and efforts to increase the ADR have been ongoing ever since.

▶ **Table 1** Characteristics of the 1221 patients undergoing screening colonoscopy and the procedures they underwent in the two groups (Exera III/190 vs. control/165 group).

Variable	190 group (n = 599)	165 group (n = 622)
Patient data		
▪ Age, mean ± SD (range), years	62.5 ± 7.0 (51 – 84)	61.9 ± 6.3 (50 – 81)
▪ Male sex, %	45.7 %	46.5 %
Sedation, n (%)		
▪ None	43 (7.2 %)	44 (7.1 %)
▪ Midazolam-based regimens	89 (14.9 %)	95 (15.3 %)
▪ Midazolam plus propofol	33 (5.5 %)	30 (4.8 %)
▪ Propofol alone	434 (72.5 %)	453 (72.8 %)
Quality of sedation, excellent/complete, %	72.8 %	74.3 %
Median (IQR) examination time, minutes		
▪ Total	12.0 (10.0 – 15.7)	12.0 (10.0 – 15.0)
▪ Introduction	4.7 (3.3 – 6.5)	4.8 (3.3 – 7.0)
▪ Withdrawal (including biopsy/polypectomy)	7.0 (5.8 – 9.0)	6.8 (6.0 – 8.3)
▪ Withdrawal (without biopsy/polypectomy)*	6.8 (6.0 – 8.3)	7.0 (6.0 – 8.0)
Cecal intubation rate, n (%)	590 (98.5 %)	608 (97.7 %)
Quality of colon preparation, %		
▪ Excellent	52.4 %	46.6 %
▪ At least fair	96.7 %	95.5 %

SD, standard deviation: IQR, interquartile range.
* Missing data on net colonoscopy times in 27 % and 34 % of patients with biopsy/polypectomy in the 190-C and 165-C groups, respectively.

There are a variety of factors that influence ADR: in addition to patient (age, sex, colon cleanliness), setting (primary/secondary screening, diagnostic), and physician factors [22], colonoscope technology has been the topic of intensive research in the last decade. Generally, studies have shown that improvements or changes to single features of colonoscope imaging technology have not consistently increased ADR [23].

Previously, we were able to show in a large study on colonoscopy quality [12], as well in a retrospective analysis of endoscopes used [11], that improvements of several features of the instrument – such as with a change from one generation to the next but one – have to be implemented before an effect on the ADR becomes obvious. This hypothesis formed the basis of the present prospective randomized trial. We compared the latest generation of colonoscopes from one company to the next but last one (Olympus 190 vs. 165), where several features have been changed or improved, such as imaging quality (1080 lines HDTV vs. 657 lines SDTV, including characteristics of the video processor), differentiation of depth of field (2 – 5 mm near and 5 – 100 mm far vs. 3 – 100 mm), resolution in near- and far-focus mode, field of view (160° near and 170° far vs. 140°), and brighter NBI.

Our results in 1200 patients show that there is some improvement of adenoma detection and yield with this two-generation change, but this did not lead to a significant ADR increase for our case number calculation. Our case number calculation assumed an increase of 7 percentage points from 20 % to 27 % to be clinically relevant based on previous studies of the group in the same setting [11]. Such assumptions are always subject to discussion, particularly given the fact that any increases in ADR are mostly due to more small and diminutive adenomas being detected. However, we think that absolute increases of 5 percentage points or less are probably irrelevant and 10 percentage points are unlikely to be achieved, judging from the majority of previous studies. In fact, the mean ADR of the present study was 28 % in the control group, instead of the assumed 20 % in previous studies of this group. This fact can be viewed in line with recent data from the German screening colonoscopy registry, which show that the mean ADR has been increasing over the years [24]. Under the results achieved with a base rate ADR of 28 % in the control group, our case number would have been sufficient to show an increase of 8 percentage points (80 % power, $P = 0.05$) over baseline. To show a significant difference of 4 percentage points as in the present study (i. e.

▶ **Table 2** Results for adenoma detection in the Exera III (190) group and control (165) group.

	190 group (n = 599)	165 group (n = 622)	*P* value	Group difference
Adenomas, n	340	293		
Patients with at least one adenoma, n	209	190		
Number of adenomas per adenoma carrier[1] (95 %CI)	1.62 (1.43 to 1.80)	1.53 (1.35 to 1.72)	0.52	0.08 (−0.17 to 0.33)
Adenoma detection rate[2] (95 %CI)	0.32 (0.26 to 0.39)	0.28 (0.22 to 0.34)	0.10	0.04 (−0.01 to 0.09)
Overall adenoma rate[3] (95 %CI)	0.57 (0.53 to 0.61)	0.47 (0.43 to 0.51)	< 0.001	0.10 (0.04 to 0.15)
Left-sided adenomas, n (%)				
▪ Within all adenomas	139 (41.1 %)	106 (36.2 %)	0.20	
▪ Within all patients	139 (23.2 %)	106 (17.0 %)	0.007	
Right-sided adenomas				
▪ Within all patients	199 (33.2 %)	187 (30.1 %)	0.24	
Adenoma subgroups[4], n (%)				
▪ < 5 mm	135 (22.5 %)	97 (15.6 %)	0.002	
▪ ≥ 5 to < 10 mm	131 (21.9 %)	125 (20.1 %)	0.45	
▪ ≥ 10 to < 20 mm	55 (9.2 %)	50 (8.0 %)	0.48	
▪ ≥ 20 mm	15 (2.5 %)	16 (2.6 %)	0.94	
▪ Flat adenomas	115 (34.5 %)	97 (34.5 %)	> 0.99	
▪ Adenomas with HGIN	7 (2.1 %)	6 (2.0 %)	0.99	
▪ SSA/P	62 (18.2 %)	81 (27.6 %)	0.005	
Hyperplastic polyps, n	100	105		
Hyperplastic polyps < 10 mm	90 (90.0 %)	98 (93.3 %)	0.39	
Carcinomas, n	10 in 9 patients	4 in 4 patients	0.14	

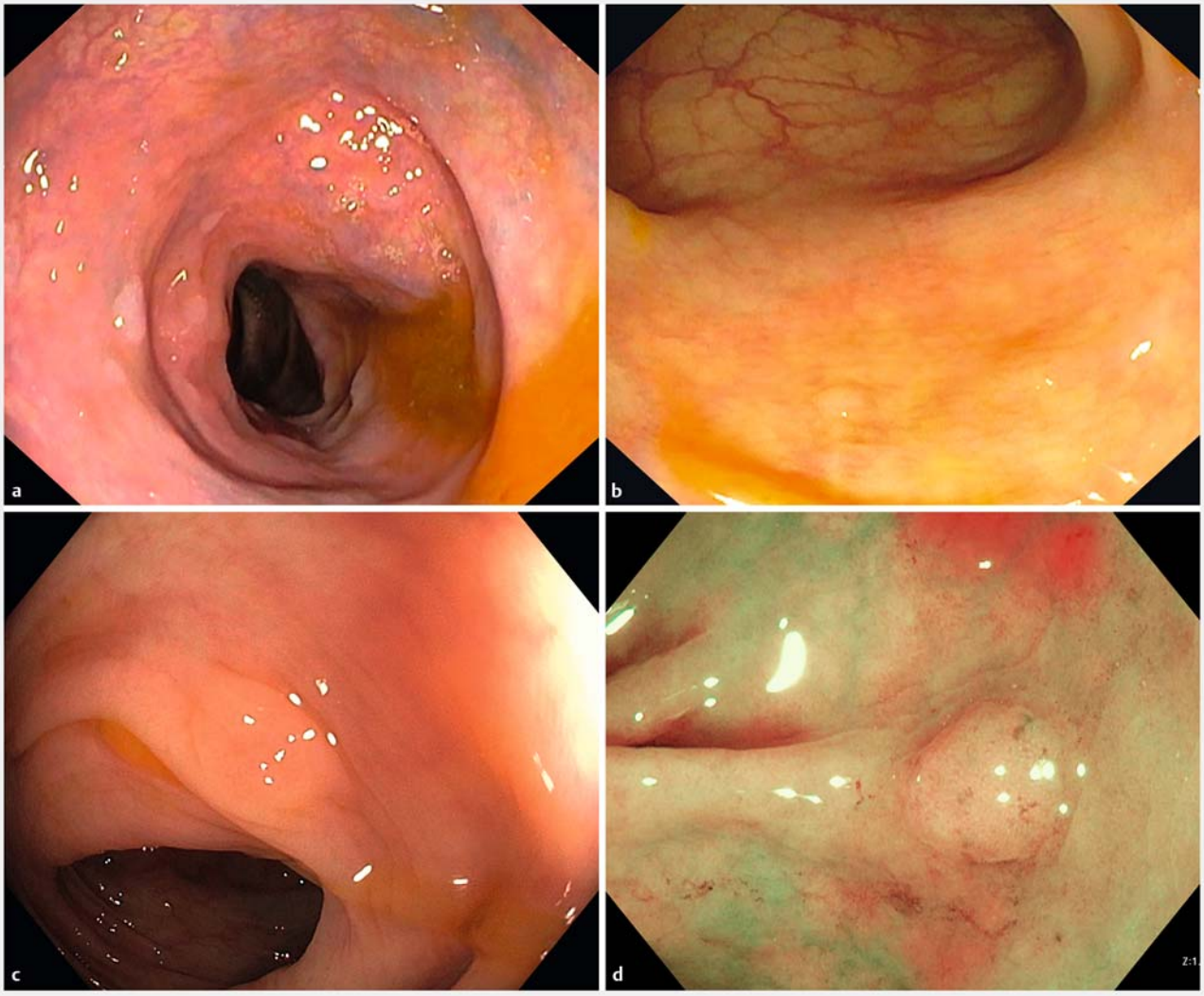
CI, confidence interval; HGIN, high grade intraepithelial neoplasia; SSA/P, sessile serrated adenoma/polyp.
[1] Mean number of adenomas found in those with at least one adenoma; estimated using regression model with respect to cluster structure.
[2] Percentage of patients with at least one adenoma; estimated using regression model with respect to cluster structure.
[3] All adenomas/all patients.
[4] For the subgroups, a few cases (2 – 12) were missing data entries so that the denominator varies slightly; furthermore, percentages are calculated for all adenomas, not for all patients.

from 28 % to 32 %), more than 4000 cases would have been required (n = 4120, 80 % power, *P* = 0.05).

On the other hand, we found a significantly higher number of adenomas, mostly small ones, in the group in which the latest generation scope was used. In fact, in the above study that showed increasing ADRs in the German screening colonoscopy registry, this was also mainly due to small adenomas being more frequently detected [24]. Especially in the screening setting, the clinical relevance of finding more small adenomas remains unclear; the outcome after removal of small (non-advanced) adenomas with regards to colorectal cancer occurrence is probably limited [25].

In a parallel tandem colonoscopy study, we were able to show more significant effects when comparing the same two generations of colonoscopes: in patients with increased risk for colorectal adenomas examined in tertiary referral centers, we found significantly decreased adenoma miss rates (17 % vs. 30 %), as well as significantly increased ADRs during the first colonoscopy (44 % vs. 36.5 %) [13].

There are several explanations for these somewhat discrepant results with regards to increases in ADR, although it is more the magnitude of the effect than contradictory results: the patient group was different in the two studies (diagnostic colonoscopy with increased risk vs. primary screening), as were the overall adenoma rates (51.6 % vs. 32.7 %). Furthermore, the setting of referral centers with a specific ambition of conducting research and publishing (good results) may lead to better results than a private-practice setting. On the other



▶ **Fig. 1** Examples of polyps imaged with the two study endoscopes (the 165 colonoscope [**a/b**] and the 190 colonoscope [**c/d**]) showing: **a/b** small hyperplastic rectal polyps in two different patients; **c** a 1-cm sessile serrated adenoma without narrow-band imaging (NBI); and **d** with NBI.

hand, the present group has sufficient experience in both endoscopy and study performance [11, 12, 14, 15, 26]. Results in general may be better in studies from referral centers, as can be seen in the example studies on colonoscopic polyp differential diagnosis comparing referral centers [27] with real-life settings [16, 28 – 30].

Finally, the study design per se may also have an influence on outcome. Tandem studies were considered to be the best option to study ADR differences in a prior review article [31]. However, analysis of the literature shows that tandem studies appear to have a much greater tendency to show significant differences in favor of the new method than do simple comparative trials, as was the case in studies using NBI [32 – 38], wide-angle scopes [8, 9], and transparent caps [39, 40]. The reasons for this are not known. It can only be speculated as to whether, for example, the risk of bias is greater in tandem studies given the lack of possibility for blinding when comparing endoscopes.

It is therefore not possible to decide which is the optimal study design when comparing techniques to increase ADR. In our opinion, at the end, we would opt for a simple comparative design as being more representative of clinical reality, given that in both situations only one colonoscopy is performed per group. Ideally, tandem and simple comparative studies should be regarded as complementary; it could be argued that only if a technique consistently shows improvements in ADR and adenoma miss rates in both types of studies can results be considered relevant, not only for referral centers but also for everyday use of the respective technique. This appears to be the case here with the present comparative study and a prior tandem study [13] showing increased adenoma yield to different extents. Therefore, we think that the combined results of the two studies have important implications for quality assurance

guidelines with regards to the necessity of technical upgrades to improve colonoscopy quality, with ADR as the most relevant surrogate variable for outcome quality.

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Competing interests

None.

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CORRECTION

Trindade AJ, Inamdar S, Smith MS et al. Learning curve and competence for volumetric laser endomicroscopy in Barrett's esophagus using cumulative sum analysis.

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In the above mentioned article the caption of Figure 2 has been corrected. This was corrected in the online version on July 26, 2018