



Time-saving polyp detection in colon capsule endoscopy: evaluation of a novel software algorithm

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Abstract

Background Colon capsule endoscopy (CCE) is a reliable method to detect colonic polyps in the well-prepared colon. As CCE evaluation can be time consuming, a new software algorithm might aid in reducing evaluation time.

Objectives The aim of the study was to evaluate whether it is feasible to reliably detect colon polyps in CCE videos with a new software algorithm the “*collage mode*” (Rapid 8 Software, Covidien/Medtronic®).

Methods Twenty-nine CCE videos were randomly presented to three experienced and to three inexperienced investigators. Videos were evaluated by applying the collage mode. Investigation time was documented and the results (≥one polyp vs. no polyp) were compared with the findings of two highly experienced central readers who read the CCE videos in the standard mode beforehand.

Results It took a median time of 9.8, 3.5, and 7.5 vs. 4.3, 4.6 and 12.5 min for experienced vs. inexperienced investigators to review the CCE videos. For detecting ≥one polyp vs. no polyp, sensitivity of 93.3%, 73.3%, and 93.3% was observed for the experienced and sensitivity of 46.7%, 33.3%, and 93.3% for the inexperienced CCE readers.

Conclusion Collage mode might allow for a quick review of CCE videos with a high polyp detection rate for experienced CCE readers. Future prospective studies should include CCE collage mode for rapid polyp detection to further prove the feasibility of practical colon polyp detection by CCE and possibly support the role of CCE as a screening tool in CRC prevention.

Keywords Colon capsule endoscopy · Polyp · Colonoscopy · Endoscopy · Capsule endoscopy · Adenoma

Introduction

Colorectal cancer is one of the most common cancers in women and men, and there are over one million newly diagnosed

cases each year [1]. Aside from general preventative measures, reliable diagnostic tools are of utmost importance in order to prevent or detect cancer—ideally in its early stages—and flexible colonoscopy is the international gold standard. However, despite tremendous efforts [2–4], the negative connotations and fear associated with prophylactic colonoscopy still prevail and prevent some patients from making use of it [5–7]. Here colon capsule endoscopy (CCE) has proven to be a reliable, less invasive technique for screening and polyp detection. In a population with increased risk for polyps and in the screening population, the polyp detection rate is similar to a flexible colonoscopy [8, 9]. Furthermore, CCE is considered the method of choice to examine the colon in case that conventional colonoscopy is not possible or remains incomplete according to the current European guidelines [10]. Albeit being an innovative and reliable diagnostic tool, the long investigation and evaluation time (up to 60 min for one video) for CCE is still a major drawback for its widespread application [8]. Intelligent software algorithms might

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help to decrease review time. The “quick view mode” (Rapid 8 Software, Covidien/Medtronic®) for example, led to a substantially reduced investigation time in capsule endoscopy investigations while having a comparable sensitivity and specificity as the normal viewing mode [11]. However, other studies found an unacceptably high miss rate for potentially important lesions using the quick view mode [12].

The software algorithm “collage mode” (Rapid 8 Software, Covidien/Medtronic®) aims to reduce investigation time of CCE by presenting multiple pre-selected details of colon capsule endoscopy images at once. Thereby, the ultimate goal would be to reduce evaluation time in a significant way in order to render back to back CCE and colonoscopy—if relevant findings in CCE warrant it—a more feasible undertaking in clinical practice.

Despite having been shown to be possible, same-day colonoscopy after CCE still is a rarity in clinical practice [13]. An integral part in strengthening the potential role of CCE as a filter tool for deciding which patients need to undergo consecutive colonoscopy for polyp resection, the CCE reading time needs to be substantially reduced and new software algorithms might aid in making this a reality. In this study, the collage mode was evaluated in a controlled trial with regard to investigation time and sensitivity of general polyp detection.

Methods

In this trial, the results of three experienced and three inexperienced CCE investigators were compared. The primary endpoints of the study were the overall reading time of CCE videos using the collage mode as well as the sensitivity of general polyp detection. We did not aim to compare the exact number of polyps detected by the investigators, and a per patient polyp detection of ≥ 1 significant polyps—defined as a polyp of ≥ 6 mm in size—led to referral of the patient for flexible colonoscopy to remove the polyp. We thus aimed to evaluate if CCE could be used as a filtering technique in the sense of a screening tool by using the time-saving collage mode that reliably identifies patients who need polyp resection. We did not aim to compare the exact number of polyps detected by the investigators.

Approval for this study was obtained by the local ethics committee of the university hospital Frankfurt prior to the beginning of the study (file number 189/14).

Software: collage mode

In the collage mode (Rapid 8 Software, Covidien/Medtronic®), relevant parts from selected images of interest are cropped and arranged in a matrix to provide an overview of the most interesting image elements from the study video. The layout contains eight rows and the maximum number of

columns that can fit on the display (dependent on the respective resolution of the display) (Fig. 1). An automated software filter preselects the pictures by identifying polypoid lesions differing in color and pattern from the regular colon mucosa and erasing redundant pictures. The review speed of the video-pictures in collage mode was controlled by scrolling individually and unidirectionally. Investigators were allowed to optionally use the FICE mode to improve polyp demarcation.

PillCam COLON 2 system

Throughout the study, we used the PillCam COLON 2 system (Given Imaging Inc., Yoqneam, Israel, now Covidien/Medtronic®). This is the second-generation ingestible capsule provided with two micro-cameras, one at the front and one at the back of the capsule. It is 11.6 mm \times 31.5 mm in size and offers an angle of vision of 172°. All images taken by the capsule are sent to a data recorder via sensors attached to the abdomen of the patient. A software package displays the images on a workstation for review and reporting of the results. The battery provides power for about 10–14 h. With movement adaptive framerate, images are taken in a slow frequency of 4/s in case of non-movement of the capsule, but framerate is increased to 35/s in the propagated capsule. In order to save battery power, the capsule takes only 4 images per minute in the stomach (“sleep mode”).

Bowel preparation and evaluation of cleanliness

In all patients, bowel preparation was conducted in accordance with a standardized cleansing protocol using polyethyenglycol (PEG) 3350-electrolytes-vitaminC solution (Moviprep®, Norgine, Marburg, Germany), Natriumpicosulfat (CitraFleet®, Recordati, Ulm, Germany), and a bisacodyl suppository (Dulcolax®, Boehringer Ingelheim, Ingelheim, Germany) (Table 1). Initially, bowel cleanliness was evaluated by using a 4-point grading scale (poor, fair, good, and excellent) by Leighton et al. [14]. Consecutively—for simplification purposes—the 4-point grading scale was then shortened to a 2-point grading scale with poor and fair results being considered as inadequate and good and excellent being considered as adequate levels of cleanliness.

Study design

Thirty randomly selected CCE videos, which had been reviewed by two independent expert CCE investigators (“central reader”) prior to the start of this study, were chosen for investigation. One video was unsuitable—due to a technical defect—which only became apparent after the selection of the 30 videos, and therefore, ultimately only 29 videos were

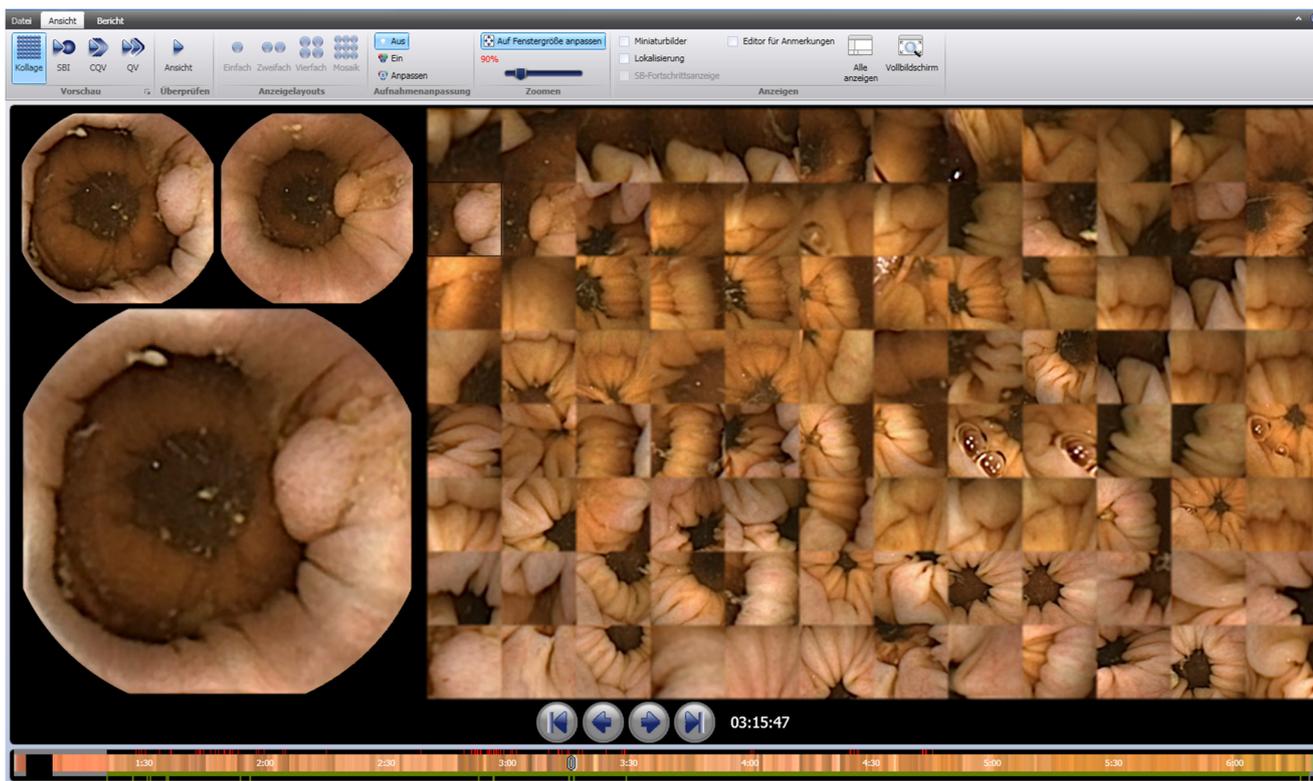


Fig. 1 Screenshot from the Rapid 8 software showing the functionality of the *collage mode*. The image presented in large on the left side is chosen by moving the computer mouse over the collage images on the right. One image before and one behind the selected image are also presented (left top).

evaluated. From these 29 CCE videos, 15 had polyp findings, whereas 14 showed normal results. The two central readers’ experiences encompassed the reading of more than 150 CCE videos. All of the CCE videos were meticulously reviewed by the CCE experts with the standard review software mode beforehand. Findings of the independent central readers were defined as the standard for the findings in the trial videos by our investigators. If there was a discrepancy in findings between the two central readers, a consensus was found by joint evaluation. All CCE videos that had been selected for the study were blinded as well as anonymized, and an ID number was given to every video. The findings of all study investigators were only un-blinded by the independent central readers

after closing the study by receiving all data files. We defined three experienced expert (A, B, C) and three inexperienced non-expert (D, E, F) CCE investigators. An “expert” was defined as an advanced gastroenterologist with experience in flexible colonoscopy of over 10 years. All “experts” had undergone a two-day intensive training course for detecting polyps at CCE and had read about 50 routine CCE videos before start of this study. The “non-expert” investigators were beginners in flexible endoscopy. They were introduced in using the Rapid 8 and “collage” software, and they received a 20-min briefing about morphology of polyps and technique of CCE and were reading three CCE videos in the standard software mode before starting the study. One of the “non-

Table 1 Bowel preparation regimen for Colon Capsule endoscopy

2 days prior to capsule intake	Ingestion of clear liquids (as much as possible) and Senna at going to bed
1 day prior to capsule intake	Liquid diet
Evening before capsule intake (6–8 pm)	1.5 l of PEG solution + 2 l of clear liquid
Morning of capsule intake (until 6:30 am)	1 l of PEG solution + 2 l of clear liquid
Start of CCE investigation (8 am)	No food intake during CCE investigation Max. 3 boosts to accelerate passage time
First boost	15–20 ml of Na picosulfate in 120 ml water with 1 l of water
Second boost	2.5 h after the first boost, 25 ml Fleet with 1 l of water

expert” CCE readers (reader F) had minor experience in flexible colonoscopy but had previously examined 25 CCE routine video cases and was thus skilled in reading CCE videos and in detecting polyps.

A total of 30 videos appeared to be an adequate sample size as this pilot study aimed to show feasibility for the “collage” mode algorithm with regard to polyp detection and to reducing CCE evaluation time. The time-saving aspect was considered as the endpoint of the study. Polyp detection was considered as an “add-on” to determine whether decreased evaluation time leads to missing relevant polyps.

CCE video analysis

All videos were analyzed in standardized conditions in a closed room excluding any disturbance during evaluating the videos by six independent investigators who were blinded to findings of the video and who reviewed the trial CCE videos in a different random sequence. The review of CCE videos commenced when a timer was started before opening the video file. Then, the investigators identified the first and the last colonic image and noted if the colon was completely visualized. All colonic polyps were marked digitally using the thumbnail function of Rapid 8 Software (Covidien/Medtronic®). After finishing the video analysis, the timer was stopped and all findings were noted on a clinical report form (CRF). For review of the CCE videos, all investigators applied the “collage” mode.

Statistical analysis

Statistical analysis was performed with BiAS (version 11.02, 2016, Epsilon Verlag, Hochheim, Darmstadt, Germany) and R (version 3.5, R Core Team (2018); R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Investigator’s review times were compared via the nonparametric Friedman test and semiparametric multiple Conover post-hoc comparisons. Nonparametric Spearman’s correlation was used to measure the association between the investigators’ review times. Fleiss’ Kappa was used to test interrater reliability. All tests were two-sided, and a p value of 0.05 was set as threshold for significance.

Results

CCE video evaluation time

It took a median (IQR) time of 9.8 (2.8–18), 3.5 (0.7–6.7), and 7.5 (2.7–14.8) vs. 4.3 (1.3–14), 4.6 (1.8–12.7), and 12.5 (4–17.1) min to review one CCE video by applying the “collage” mode for experienced vs. inexperienced investigators (A, B,

C, and D, E, F), respectively. The median evaluation time for all experienced readers was 7.56 (3.5–10.1) and 5.4 (5.4–11.9) for the inexperienced investigators. Each investigator reviewed all 29 CCE videos. The investigator’s review times differed significantly ($p < 0.0001$) in global and post-hoc tests ($p < 0.0001$ – $p = 0.004$), except between D and E ($p > 0.2$), the most inexperienced investigators. Bivariate Spearman’s correlation shows that review times correlated significantly ($p = 0.0001$ – $p = 0.0371$, with a correlation coefficient r between 0.38 and 0.68, data not shown) between pairs of investigators, except for A and F ($p = 0.09$). This indicates that there are videos that take longer to review in general (see also Table 2). In comparison, the review of CCE videos using the standard mode by the central reader lasted a median time of 49 min.

Polyp detection

For detecting at least one polyp vs. no polyp, sensitivity of 93.3%, 73.3%, and 93.3% was observed for the experienced investigators A, B, and C, respectively. Sensitivity of 46.7%, 33.3%, and 93.3% was found in the inexperienced investigators D, E, and F, respectively. Specificity was 85.7% (A), 92.9% (B), and 92.9% (C) for experienced and 85.7% (D), 100.0% (E), and 85.7% (F) for inexperienced investigators (Table 2). The positive and negative predictive values were 0.91 and 0.86 for experienced investigators and 0.87 and 0.67 for inexperienced investigators. Fleiss’ Kappa for all six investigators was 0.51 (95% CI, 0.22–0.80; $p = 0.0005$), which indicates a moderate agreement according to Landis and Koch [15], 0.77 (95% CI, 0.41–1.00; $p < 0.0001$) for the experienced investigators, which indicates a substantial agreement, respectively, and 0.29 (95% CI, –0.11–0.69; $p = 0.16$) for the inexperienced users (no significant agreement). Comparing the number of detected polyps, the overall Fleiss’ Kappa was 0.28 (95% CI, 0.06–0.51; $p = 0.01$, fair agreement), 0.44 (95% CI, 0.18–0.70; $p = 0.0010$, moderate agreement) for the experienced users and 0.10 (95% CI, –0.23–0.44; $p > 0.2$, no significant agreement) for the inexperienced investigators. All patients with suspicion of a significant polyp at CCE had undergone flexible ileo-colonoscopy, and all polyps seen at the CCE videos had been confirmed by flexible colonoscopy. Interestingly, the number of polyps detected by CCE differed from the number of polyps detected by conventional colonoscopy. However, these results did not prove to be statistically significant ($p > 0.2$). Notably, the inexperienced investigator (reader F) with experience in small bowel capsule endoscopy reading, but with only minor experience in flexible colonoscopy, affected a sensitivity of 93.3% for polyp detection, comparable to the sensitivity found in the experienced reader group. In all cases, the median

Table 2 Correlation of CCE evaluation time and overall polyp detection

	A	B	C	D	E	F
Cases of correct polyp/no polyp/detection? <i>n</i> /total	24/29	25/29	26/29	18/29	21/29	25/29
Median evaluation time in minutes median (range)	9.8 (2.8–18)	3.5 (0.7–6.7)	7.5 (2.7–14.8)	4.3 (1.3–14)	4.6 (1.8–12.7)	12.5 (4–17.1)
Sensitivity %	93.33	73.33	93.33	46.66	33.33	93.33
Specificity %	85.71	92.86	92.86	85.71	100	85.71
Short* evaluation time and incorrect finding <i>n</i> /total	2/29	5/29	1/29	6/29	6/29	4/29
Short evaluation and correct finding <i>n</i> /total	13/29	11/29	12/29	9/29	10/29	11/26
Median evaluation time in correct findings in minutes median (range)	9.9 (3.2–18)	3.9 (1.2–6.7)	7.5 (2.8–14.8)	5 (1.5–14)	5.1 (2–12.7)	12.5 (4–17.1)
Median evaluation time in incorrect findings in minutes median (range)	5.2 (2.8–7.5)	3.1 (0.7–3.5)	7.3 [#]	3.3 (1.3–4)	2.5 (1.8–4.1)	8 (4–12)

*A short evaluation time was defined as being below the investigator's median evaluation time

[#] Only one case was documented the respective time for this case was provided

evaluation time was lower in incorrect cases than in the overall median evaluation time of the videos. In general, it could be observed that investigation times below 8 min lead to higher failure rates (Table 2).

Bowel cleanliness

The level of bowel cleanliness in the CCE videos was described as adequate in 55% (A), 100% (B), 45% (C), 82% (D), 76% (E), and 17% (F). However, there was no significant agreement about the rating of cleanliness ($p > 0.2$).

Discussion

In preventing colorectal cancer—one of the most commonly diagnosed worldwide—flexible colonoscopy is considered the gold standard for polyp detection. Less invasive methods that might increase the patient's comfort could improve currently low acceptance rates for CRC screening [10, 16–18]. Colon capsule endoscopy is considered a reliable tool for the detection of colonic polyps [10]. In per patient analysis, sensitivity for detecting polyps is as high as 84–94% in prospective studies [8, 19–21] and has therefore become a valid alternative

especially for patients unable or unwilling to undergo colonoscopy. Furthermore, CCE is the preferred alternative modality to visualize the entire colon for patients with a previously incomplete colonoscopy [22–24].

In terms of sensitivity and specificity, CCE is comparable to computed tomographic colonography (CTC), another diagnostic alternative to flexible colonoscopy [18, 25, 26]. However, in contrast to CTC or other colon visualization methods like cross-sectional imaging techniques, CCE operates without radiation or contrast agent and thus avoids radiation—and gadolinium-associated toxicity. Furthermore, CCE can be provided by the treating gastroenterologist himself, thus possibly reducing time to diagnosis and being more practical especially if polyp ablation is needed.

The major limitation of CCE is the long examination time that significantly impedes the widespread application of this method [9]. The standard review time for the CCE video takes up to 60 min [9, 27], a time span that could alternatively be filled by performing at least one conventional colonoscopy. One software algorithm aiming to reduce evaluation time is the quick view mode. This algorithm operates by scanning all images and consecutively rates them by level of significance. It thus provides a shortened video which only provides images that should be interesting to the reader—instead of the entirety

of all CCE frames. However, studies have shown that relevant findings might be missed [12].

In this post-hoc CCE reading pilot trial, we aimed to determine whether a different software algorithm—the so-called collage mode—might aid in reducing time for CCE video evaluation while maintaining a reliable detection rate for relevant colon polyps. To the best of our knowledge, this study is first to evaluate this viewing mode. We observed that when applying this algorithm the evaluation time was considerably reduced to on average 7 min in comparison to a reading time of up to 60 min in the standard evaluation mode. At least one polyp was detected in >90% of cases in three of the six investigators who were experienced in reading CCE videos (sensitivity of 93.3% for readers A, C, F), although only two of these investigators were highly experienced in flexible colonoscopy (readers A, C). Two investigators (readers D, E) who were without any experience in either flexible colonoscopy or in CCE video reading detected colonic polyps in <50% (sensitivity of 46.6 and 33.3% respectively) despite using the same software mode. Training in CCE reading that would preferably include expert instructions in a hands-on training course together with some experience by primarily responsible reading CCE videos seems therefore crucial for valid use of the collage mode. Experience in flexible colonoscopy could help to understand polyp morphology, but might not suffice to read CCE. That might be due to the difference in visualizing the colon: At flexible colonoscopy, the colon is dilated by gas insufflation, but CCE visualizes the colonic mucosa that is submerged by the purgative. Thus, delineation of polyps might be different: Some polyps could appear flat in colonoscopy but may protrude into the lumen in CCE [28]. Still, further studies are needed in order to better understand the extent of training and instructions of CCE needed to achieve valid polyp detection at using standard CCE reading mode and collage mode, though.

The rather small number of CCE videos can be considered as a limitation of our study. Other critique points might be for one the inconsistent results for bowel cleanliness, possibly due to different experience levels of the investigators and that the exact number of polyps was not determined. However, the primary goal of this study was to investigate whether using the collage mode and thus reducing evaluation time could aid in reliably identifying patients who need polyp ablation. We therefore elected not to compare the exact number of polyps detected by the investigators. Still, further prospective trials investigating sensitivity and specificity in correlation colonoscopy are warranted.

Problematics concerning differences in intra- and inter-observer evaluation of CCE have been recently discussed and ought not to be underestimated [29]. Still, our study has its merits as we were able to show that indeed with the help of the collage mode investigation time was considerably reduced while maintaining—at least for experienced CCE readers—a

high rate of polyp detection which leads to referral of the patients for endoscopic polyp removal. Our results thus might on the one hand encourage prospective studies including CCE collage mode for quick polyp detection and on the other hand help in making CCE available for a larger demographic due to reduced evaluation time. CCE could therefore serve as a diagnostic tool for polyp detection for patients unable or unwilling to undergo prophylactic colonoscopy [18]. Polyp detection in CCE will then hopefully motivate patients to undergo endoscopic removal.

Author contributions The authors have contributed to the manuscript by planning the study (JH, JPL JA, NF, MK, MF), collecting the data (JH, JPL, JA, JM, AT, MP, MK, MF), analysis and interpretation of data (JH, JA, NF, MF), and preparation (JH, JA, AK) and revision of the manuscript (all authors).

Compliance with ethical standards

Approval for this study was obtained by the local ethics committee of the university hospital Frankfurt prior to the beginning of the study (file number 189/14).

Conflict of interest Jörg Albert, Michael Farnbacher, Johannes Hausmann, Michael Philipper, and Andrea Tal report lecturer fees from Covidien/Medtronic® all outside of the submitted work.

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